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The references in this volume are provided for informational purposes and are optional reading.

18. "Efficacy and Safety of Single and Multiple Doses of Pseudoepedrine in the Treatment of Nasal Congestion Associated with Common Cold," *American Journal of Rhinology* 19:25-31, 2005.
19. "Efficacy of a Paracetamol-Pseudoephedrine Combination for Treatment of Nasal Congestion and Pain-Related Symptoms in Upper Respiratory Tract Infection," *Current Medical Research and Opinions* 22:2411-2418, 2006.
20. "Nasal Dyspnea: The Place of Rhinomanometry in its Objective Assessment," *American Journal of Rhinology* 18:41-46, 2004.
21. "The Cardio-Circulatory Effects in Man of Neo-Synephrin (1-alpha-hydroxy-beta-methylamino-3-hydroxy-ethylbenzene hydrochloride)," *Journal of Clinical Investigation* 21:1-12, 1942.
22. June 1968 Memo to Bird, J.G. from H. Stander.
23. January 1967 Memo to Luduena form H. Stander.
24. "Physiologic and Pharmacologic Studies on Nasal Airway Resistance (R_N)," The Proprietary Association. Current Research Methodology in the Evaluation of Proprietary Medicines: *Proceedings of a conference sponsored by the Scientific Development Committee of the Proprietary Association*, 1971
25. "A Comparison of the Cardiovascular Effects of Phenylpropanolamine and Phenylephrine Containing Proprietary Cold Remedies," *British Journal of Clinical Pharmacology* 32:705-711, 1991.
26. June 1968 Memo to Hulme from J.G. Bird.
27. "Modification by Monoamine Oxidase Inhibitors of the Effect of Some Sympathomimetics on Blood Pressure," *British Medical Journal* 2:75-78, 1967.
28. "Physiologic and pharmacologic studies on nasal airway resistance," *Clinical Pharmacology and Therapeutics* 14:146, 1973.
29. "Pharmacokinetics of Oral Decongestants," *Pharmacotherapy* 13::116S – 128S, 1993.
30. "Analysis of Phenylephrine in Plasma: Initial Data about the Concentration-Effect Relationship," *European Journal of Clinical Pharmacology* 30:427-431, 1986.
31. "Some Studies of a Sustained Release Principle," *Journal of Pharmaceutical Sciences* 52:259-263, 1963.
32. *Federal Register* 41:38399, 1976.
33. "Pharmacokinetics of ^{3}H-Phenylephrine in Man," *European Journal of Clinical Pharmacology* 21:335-341, 1982

B. Attachment - Minutes for the Joint Meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee, October 18-19, 2007

C. Pulmonary Review

1. "Anatomy and Physiology of the Nose and Control of Nasal Airflow," *Middleton's Allergy, Principles & Practice*. 6th ed. Philadelphia, 2003, Mosby, p 775-787
2. "Acoustic Rhinometry in the Practice of Allergy," *Ann Allergy Asthma Immunol* 2006; 97:745-52.
3. "Assessment of Nasal Cycle by Aacoustic Rhinometry and Rhinomanometry," *Otolaryngol Head Neck Surg* 2003; 128:510-6.
4. "Diagnosis and Management of Rhinitis: Complete Guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology," *Ann Allergy Asthma Immonul* 1998; 81:478-518.

3. Draft Guidance (2718) Allergic Rhinitis: Clinical Development Programs for Drug Products

1. Federal Register Publications

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 341]

[Docket No. 76N–0052]

OVER-THE-COUNTER DRUGS

Establishment of a Monograph for OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products

The Food and Drug Administration (FDA) proposes to establish conditions under which over-the-counter (OTC) cold, cough, allergy, bronchodilator and antiasthmatic drugs are generally recognized as safe and effective and not misbranded, based on the recommendations of the Advisory Review Panel on Over-the-Counter (OTC) Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products; comments by December 8, 1976.

Pursuant to Part 330 (21 CFR Part 330), the Commissioner of Food and Drugs received on March 3, 1976, the report of the Advisory Review Panel on Over-The-Counter (OTC) Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products. In accordance with § 330.10(a)(6) (21 CFR 330.10(a)(6)), the Commissioner is issuing (1) a proposed regulation containing the monograph recommended by the Panel establishing conditions under which OTC cold, cough, allergy, bronchodilator and antiasthmatic drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel that they would result in the drugs not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel that the available data are insufficient to classify such conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel to the Commissioner. The summary minutes of the Panel meetings are on public display in the office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852.

The purpose of issuing the unaltered conclusions and recommendations of the Panel is to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The Commissioner has not yet fully evaluated the report, but has concluded that it should first be issued as a formal proposal to obtain full public comment before any decision is made on the recommendations of the Panel. The report of the Panel represents the best scientific judgment of the members. The report has been prepared independently of FDA and does not necessarily reflect the agency position on any particular matter contained therein. After a careful review of all comments submitted in response to this proposal, the Commissioner will issue a tentative final regulation in the FEDERAL REGISTER to establish a monograph for OTC cold, cough, allergy, bronchodilator and antiasthmatic drug products.

In accordance with § 330.10(a)(2) (21 CFR 330.10(a)(2)), all data and information concerning OTC cold, cough, allergy, bronchodilator and antiasthmatic drug products submitted for consideration by the Advisory Review Panel have been handled as confidential by the Panel and FDA. All such data and information shall be put on public display at the office of the Hearing Clerk, Food and Drug Administration, on or before October 12, 1976, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality shall be submitted to FDA, Bureau of Drugs, Division of OTC Drug Products Evaluation (HFD–510), 5600 Fishers Lane, Rockville, MD 20852.

Based upon the conclusions and recommendations of the Panel, the Commissioner proposes, upon publication of the final regulation:

1. That the conditions included in the monograph on the basis of the Panel's determination that they are generally recognized as safe and effective and are not misbranded (Category I) be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

2. That the conditions excluded from the monograph on the basis of the Panel's determination that they would result in the drug not being generally recognized as safe and effective or would result in misbranding (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER, regardless whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient (Category III) to classify such conditions either as Category I—generally recognized as safe and effective and not misbranded, or as Category II—not being generally recognized as safe and effective or would result in misbranding, be permitted to remain in use for not longer than 2 to 5 years (for the specific conditions specified in this document) after the date of publication of the final monograph in the FEDERAL REGISTER, if the manufacturer or distributor of any such drug utilizing such conditions in the interim conducts tests and studies adequate and appropriate to satisfy the questions raised with respect to the particular condition by the Panel. The period of time within which studies must be completed will be carefully reviewed by the Commissioner after receipt of comments on this document and will probably be revised downward.

This proposal sets forth the conclusion of the Advisory Review Panel on Over-the-Counter (OTC) Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products that several ingredients are safe and effective for OTC use which heretofore have been limited to prescription use or classified for OTC use at a dosage level lower than that recommended by the Panel. The Commissioner is aware that a number of questions have been presented to the agency regarding the OTC marketing status of ingredients or amounts of ingredients previously limited to prescription use prior to finalization of an applicable monograph for the ingredients. The reclassification of ingredients from prescription to OTC status presents important issues that need careful and special consideration.

Accordingly, the Commissioner proposed, in the FEDERAL REGISTER of December 4, 1975 (40 FR 56675), a policy to clarify the marketing status of (1) all ingredients currently restricted to prescription use which an OTC advisory panel recommends as Category I (safe and effective), Category II (not safe and effective), or Category III (the available data are insufficient to classify the drug); and (2) the use of active ingredients at dosage levels higher than that available in any OTC drug product.

The Commissioner also advised in the preamble to the proposal in the December 4, 1975 FEDERAL REGISTER that he may indicate his disagreement with the panel's recommendation(s) regarding specific ingredients proposed for Category I, e.g., ingredients having manufacturing or formulation problems or unresolved questions concerning a potential for abuse or misuse; and he may make a tentative determination that an approved new drug application (NDA) is required for marketing an OTC product containing such ingredients. The Commissioner acted on this proposal by final regulation published in the FEDERAL REGISTER of August 4, 1976 (41 FR 32580).

The Commissioner has reviewed those ingredients included in the Panel's recommendations that are currently limited to prescription use or classified for OTC use at a dosage level lower than that recommended by the Panel. He has made an initial determination that an approved NDA is required for OTC marketing of promethazine for any indication, for OTC marketing of doxylamine succinate as an antihistamine at a dosage level in excess of 7.5 milligrams (mg), and for OTC marketing of diphenhydramine as an antihistamine. The Commissioner is deferring his decision on the Panel's recommendation that diphenhydramine be considered generally recognized as safe and effective for OTC use as an antitussive until the agency has had an opportunity to rule on a supplemental NDA now pending for OTC use of an antitussive product containing diphenhydramine. The Commissioner has made an initial determination to accept the Panel's recommendations on OTC use of a number of ingredients among which are chlorpheniramine, pseudoephedrine, theophylline, and methoxyphenamine. However, the Commissioner wishes to raise several pertinent points regarding these drugs, and they are fully explained below.

Promethazine. The Panel recommended classification of the ingredient promethazine as a Category I OTC antihistaminic drug. This ingredient is presently a component of drug products that are the subject of approved NDA's for prescription use as antihistamines, as

sedatives, as antiemetics, as adjuncts with narcotics for preoperative sedation, and in the postoperative management of pain. Promethazine is the only antihistaminic drug reviewed by the Panel that is chemically identified as a phenothiazine derivative; no ingredients in this class are currently available for OTC use. Promethazine, like other phenothiazines, is known to produce certain serious adverse effects, including agranulocytosis, thrombocytopenia, hypoplastic anemia, extrapyramidal symptoms, and hypotension (*AMA Drug Evaluations*, 2d Ed., p. 497), although it may produce these less frequently than do other phenothiazines. Although these adverse effects are of considerable concern, the major consideration relates to the effects of promethazine on the central nervous system (CNS). Promethazine is known to have a hypnotic effect more conspicuous than that of the other antihistaminics (see Krantz and Carr, *The Pharmacologic Principles of Medical Practice*, 8th Ed., p. 818), a problem sufficient to cause the Panel to recommend a warning, "may cause marked drowsiness," a warning not required for OTC antihistamines in general. Overdosage is thus potentially a problem with promethazine, especially for children. Children also seem particularly liable to develop such CNS adverse reactions as disturbances of the psyche, changes in sensorium, evidence of extrapyramidal disturbances, convulsions, and, rarely, coma and death. The Commissioner notes that other OTC antihistamines are available that are as effective as promethazine and less hazardous. Thus the risk of adverse effects from OTC availability of this ingredient is not justified in the absence of an offsetting benefit in the form of therapeutic superiority in comparison with antihistamine ingredients already marketed OTC.

Doxylamine succinate. The Panel recommended classification of the ingredient doxylamine succinate as a Category I OTC antihistaminic drug at the 7.5 to 12.5 mg dosage level. This ingredient is presently the subject of an approved NDA for prescription use, and for OTC use at the 7.5 mg dosage level, for several indications, including the management of perennial and seasonal rhinitis and vasomotor rhinitis pursuant to the requirements of § 310.201(a)(13) (21 CFR 310.201(a)(13)). The Commissioner concludes that doxylamine succinate should continue to be classified as a new drug and a prescription drug at dosage levels in excess of 7.5 mg. The Commissioner makes this determination because other OTC antihistaminic agents are available that are safer than doxylamine succinate at that dosage level.

Doxylamine succinate is a member of the ethanolamine class of antihistamines. As noted in the *AMA Drug Evaluations*, 2d Ed., p. 493, this class of drugs exhibits a high incidence of drowsiness compared with the other classes of antihistamines (ethylenediamines and alkylamines). As noted in the proposal regarding OTC sleep-aid drug products, published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292), about 50 percent of those persons receiving conventional antihistamine treatment doses of drugs in the ethanolamine class experienced drowsiness. In addition to the pronounced tendency to induce sedation, drugs in this group also possess significant atropine-like activity. Therefore, the Commissioner concludes that doxylamine succinate should remain a prescription new drug ingredient at the dosage levels greater than 7.5 mg.

Diphenhydramine hydrochloride. Diphenhydramine hydrochloride is the active ingredient in several products with approved NDA's. All such products are limited to prescription use. The Panel recommended that diphenhydramine hydrochloride be classified in Category I for antihistaminic use at 25 to 50 mg, which is the usual prescription dosage level. Diphenhydramine hydrochloride, like doxylamine succinate, is a member of the ethanolamine class of antihistamines. It, too, has a pronounced tendency to produce sedation in a high proportion of those persons who take it (*AMA Drug Evaluations*, 2d Ed., p. 493). For this reason, the Commissioner concludes that diphenhydramine hydrochloride should remain a prescription new drug ingredient and not be available for use as an OTC antihistamine. No diphenhydramine hydrochloride product is currently marketed OTC as an antihistamine at any dosage level.

The Panel also recommended that diphenhydramine hydrochloride be classified in Category I for OTC use as an antitussive. Diphenhydramine hydrochloride is the active ingredient in a cough syrup product now being marketed OTC. The currently effective NDA for this product limits it to prescription use and labels it as an expectorant only. The holder of the NDA has submitted a supplemental NDA that contains data in support of a claim that the product is safe and effective for use as an antitussive. The supplemental NDA also requests that the product be approved for OTC use. The Commissioner has concluded that the marketing status of diphenhydramine hydrochloride as an antitussive should be resolved by first considering the approvability of this supplemental NDA. After that, he will address the Panel's recommendation that diphenhydramine hydrochloride be considered generally recognized as safe and effective for OTC use as an antitussive.

The agency will rule on the pending supplemental NDA in the near future. The Commissioner advises that if the supplemental NDA is denied because diphenhydramine hydrochloride in the amount present in that product is not considered safe and effective for OTC use as an antitussive, he will at that time issue a notice in the FEDERAL REGISTER stating his disagreement with the Panel's recommendation that diphenhydramine hydrochloride be classified in Category I for OTC antitussive use. In that event, any such product marketed OTC would thereupon be subject to immediate regulatory action, in accordance with the enforcement policy announced in the FEDERAL REGISTER of August 4, 1976 (41 FR 32580). If the supplemental NDA is approved, the Commissioner may nevertheless conclude that the safety and/or effectiveness of antitussive products containing diphenhydramine hydrochloride has not achieved general recognition in the scientific community, and he may state such conclusion by notice in the FEDERAL REGISTER when the supplemental NDA is approved or at a later time, e.g., in the preamble to the tentative final monograph.

The Commissioner notes that the marketing status of diphenhydramine hydrochloride as an antihistamine raises different issues from those surrounding its OTC use as an antitussive. The indications, dosage levels, and number of available effective alternatives are different depending on the condition for which diphenhydramine hydrochloride is to be used. Also, the effectiveness of the ingredient is established in relation to antihistaminic use, but has not yet been ruled on in the context of the pending supplemental NDA for OTC use of a cough syrup product. Accordingly, the Commissioner's initial decision not to accept the Panel's recommendation for Category I classification of diphenhydramine hydrochloride for use as an antihistamine is independent of his decision on its status as an antitussive, although, obviously, some of the underlying factual considerations are common to each.

Chlorpheniramine, pseudoephedrine, theophylline, and methoxyphenamine. The Panel recommended that chlorpheniramine as an OTC antihistamine and pseudoephedrine as an OTC oral nasal decongestant be available at dosage levels twice those currently permitted for OTC use. Although he does not disagree with these recommendations at this time, the Commissioner is concerned that consumers accustomed to purchasing a particular product may not be aware of the increased amount of active ingredient per dosage unit. The Commissioner concludes that consumers should be fully informed about the increased dosage. He has determined, therefore, that all manufacturers who elect to reformulate their marketed products shall clearly indicate any increased dosage level on the principal display panel of each product. He further suggests that, in the case of tablet formulations, scored tablets be available to assist the consumer in achieving a lower dosage, if one is desired.

The Panel further recommended that theophylline and methoxyphenamine be made available OTC as single ingredients. The Commissioner does not contest the judgment of the Panel regarding the safety of these ingredients. However, he points out that he believes there is a scientific issue whether the recommended dosage levels are therapeutically effective for a significant identifiable population of asthmatics. Therefore, these two ingredients are currently undergoing extensive review within the agency. Consequently, the decision of the Panel may be subject to modification in the tentative final monograph.

The Commissioner invites full public comment on all of the conclusions and

recommendations of the Panel, and on his own specific conclusions regarding promethazine, doxylamine succinate, diphenhydramine, chlorpheniramine, pseudoephedrine, theophylline, and methoxyphenamine.

The Commissioner has reviewed the potential environmental impact of the recommendations and proposed monograph of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products and has concluded that the Panel's recommendations and proposed monograph will not significantly affect the quality of the human environment and that an environmental impact statement is not required. The Commissioner has also considered the inflation impact of the Panel's recommendations and proposed monograph, and no major inflation impact has been found, as defined in Executive Order 11821, OMB Circular A-107, and the Guidelines issued by the Department of Health, Education, and Welfare. Copies of the environmental and inflation impact assessments are on file with the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852.

The conclusions and recommendations in the report of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products follow:

In the FEDERAL REGISTER of January 5, 1972 (37 FR 85), the Commissioner of Food and Drugs announced a proposed review of the safety, effectiveness and labeling of all OTC drugs by independent advisory review panels. On May 8, 1972, the Commissioner signed the final regulations providing for the OTC drug review under § 330.10 published in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464), which were made effective immediately. Pursuant to these regulations the Commissioner issued a request for data and information on all cold, cough, allergy, bronchodilator and antiasthmatic (CCABA) active ingredients in drug products, in the FEDERAL REGISTER of August 9, 1972 (37 FR 16029).

The Commissioner appointed the following Panel to review the data and information submitted and to prepare a report on the safety, effectiveness, and labeling of OTC cold, cough, allergy, bronchodilator and antiasthmatic ingredients pursuant to § 330.10(a)(1):

Francis C. Lowell, M.D., Chairman
Hylan A. Bickerman, M.D.
Halla Brown, M.D.
Robert K. Chalmers, Ph.D.
Mary Jo Reilly, M.S.
James R. Tureman, M.D.
Colin R. Woolf, M.D.

The Panel was first convened on November 6, 1972, in an organizational meeting. Working meetings were held on December 11 and 12, 1972; January 23 and 24, February 28 and March 1, April 5 and 6, May 10 and 11, June 19 and 20, September 25 and 26, October 31 and November 1, December 6 and 7, 1973; January 8 and 9, March 19 and 20, June 12 and 13, September 11 and 12, October 31, November 1, December 3 and 4, 1974; January 30 and 31, April 3, 4 and 5, May 15 and 16, July 17 and 18, September 24 and 25, November 19, 20 and 21, and December 17, 18 and 19, 1975; February 2, and March 2 and 3, 1976.

Two nonvoting liaison representatives served on the Panel. Mrs. Anita Ohlhausen, nominated by an ad hoc group of consumer organizations, served as the consumer liaison and Joseph L. Kanig, Ph. D., nominated by the Proprietary Association, served as the industry liaison. The following employees of the Food and Drug Administration served: Anna L. Standard, M.D., Executive Secretary until March 26, 1974 followed by Joel Aronson, R. Ph.; Thomas D. DeCillis, R. Ph., Panel Administrator; Recie Bomar, R. Ph., Drug Information Analyst until February, 1973 followed by Lloyd G. Scott, R. Ph. until May, 1974 followed by Gary P. Trosclair, R. Ph.

In addition to the Panel members and liaison representatives, the following individuals were given an opportunity to appear before the Panel to express their views either at their own or at the Panel's request:

Paul Bass, Ph. D.
C. Warren Bearman, M.D.
John Behrman, M.D.
Richard C. Brogle, Ph. D.
C. Edward Buckley III, M.D.
A. Lee Caldwell, Jr., Ph. D.
Robert B. Choate
Sanford Chodosh, M.D.
John T. Connell, M.D.
Joseph Dresner
Constantine Falliers, M.D.
Arthur D. Flanagan, M.D.
Spencer Free, Ph. D.
Arthur Grollman, M.D.
Robert M. Hodges
George F. Hoffnagle, Sc. D.
Clarence Imboden, M.D.
Charles Janeway, M.D.
Anita Johnson, Esq.
Stuart J. Land, Esq.
Ben Marr Lanman, M.D.
Vincent D. Larkin, M.D.
Louie G. Linarelli, M.D.
Jennifer Loggie, M.D.
S. J. London, M.D.
Leslie M. Lueck, M.D.
Guillermo Martinez
John McLean, M.D.
Fletcher B. Owen, M.D.
Elias W. Packman, Sc. D.
Joseph Page, Esq.
Joseph J. Pittelli, M.D.
William R. Pool
Thomas W. Richards, M.D.
Norman Salik, M.D.
Robert T. Scanlon, M.D.
Daniel L. Shaw, Jr., M.D.
Alex Silverglade, M.D.
Joseph Smith, M.D.
Alfred E. Sutherland, Esq.
Garret W. Swenson, Esq.
M. L. Thomson, M.D.
Sumner Yaffee, M.D.

No person who so requested was denied an opportunity to appear before the Panel.

The Panel has thoroughly reviewed the literature, and the various data submissions, has listened to additional testimony from interested parties and has considered all pertinent data and information submitted through March 3, 1976 in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel's findings with respect to these classes of drugs are set out in three categories:

Category I. Conditions under which cold, cough, allergy, bronchodilator and antiasthmatic products are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which cold, cough, allergy, bronchodilator and antiasthmatic products are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

The Panel recommends the following for each group of drugs:

1. That the conditions included in the monograph on the basis of the Panel's determination that they are generally recognized as safe and effective and are not misbranded (Category I) be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

2. That the conditions excluded from the monograph on the basis of the Panel's determination that they would result in the drug not being generally recognized as safe and effective or would result in misbranding (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER, regardless of whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient (Category III) to classify such conditions either as Category I—generally recognized as safe and effective and not misbranded; or as Category II not being generally recognized as safe and effective or would result in misbranding, be permitted to remain in use for a period of time justified in the report of 2, 3, 4 or 5 years for the specific conditions after the date of publication of the final monograph in the FEDERAL REGISTER, if the manufacturer or distributor of any such drug utilizing such conditions in the interim conducts tests and studies adequate and appropriate to satisfy the questions raised with respect to the particular condition by the Panel.

I. Submission of Data and Information

Pursuant to the notice published in the Federal Register of August 9, 1972 (37 FR 16029) requesting the submission of data and information on cold, cough, allergy, bronchodilator and antiasthmatic (CCABA) drugs, the following firms made submissions relating to the indicated products:

A. SUBMISSIONS BY FIRMS

Firm	*Marketed products*
Abbott Laboratories, North Chicago, Ill. 60064.	Calcidrine Syrup, Quelidrine Cough Syrup.
Block Drug Co., Inc., Jersey City, N.J. 07302.	BC All Clear.
Boericke & Tafel, Inc., Philadelphia, Pa. 19107.	B & R Dictan Cough Syrup, B & R Tablets No. 241.
Breon Laboratories, Inc., New York, N.Y. 10016.	Bronkotabs, Bronkotabs-HAFS, Broncholixir.
Calgon Consumer Prod., Co., Inc., Pittsburgh, Pa. 15230.	Sucrets Cold Decongestant Formula, Sucrets Cough Control Formula, Sucrets Sore Throat Lozenges.
Chesebrough-Pond's, Inc., Trumbull, Conn. 06611.	Cold-Team-24 Daytime Tablets, Cold-Team-Nighttime Liquid, Pertussin 8-Hour Cough Formula, Pertussin Medicated Vaporizer, Pertussin Plus Night-Time Cold Medicine, Pertussin Wild Berry Cough Syrup.
Ciba-Geigy Corp., Summit, N.J. 07901	Otrivin Nasal Solution, Otrivin Nasal Spray, Otrivin Pediatric Nasal Solution, Otrivin Pediatric Nasal Spray, Privine Nasal Solution, Privine Nasal Spray.
Colgate-Palmolive Co., Piscataway, N.J. 08854.	Congestaid Aerosol.
Creomulsion Co., Atlanta, Ga. 30301	Cough Chek, Colchek, Creomulsion Cough Medicine, Creomulsion Cough Medicine for Children, Creozets Cough and Throat Lozenges.
Dorsey Laboratories, Lincoln, Nebr. 68501	Chexit Tablets, Dor-C Tablets, Dorcol Pediatric Cough Syrup, Triaminic Expectorant, Triaminic Syrup, Triaminicin Nasal Spray, Triaminicin Tablets, Triaminicol Cough Syrup, Tussagesic Suspension, Tussagesic Tablets, and Ursinus Tablets.
The Dow Chemical Co., Zionsville, Ind. 46077.	Novahistine DH, Novahistine Elixir, Novahistine Expectorant, Novahistine Fortis Capsules, Novahistine Melet Tablets, 2/G, and 2G/DM.
Drew Laboratories, New York, N.Y. 10016	Bronkaid Mist, Bronkaid Tablets.
F & F Laboratories, Inc., Chicago, Ill. 60632.	F. & F. Original Formula Cough Lozenges.
Father John's Medicine Co., Inc., Lowell, Mass. 01853.	Father John's Medicine for Cough and Colds.
G. E. Laboratories, Inc., Shamokin, Pa. 17872.	Troutman's Cough Syrup.
Glenbrook Laboratories, New York, N.Y. 10016.	Breacol Decongestant Cough Medication with Neo-Synephrine.
Hall Brothers, Radcliffe, Manchester England.	Hall's Honey-Lemon Cough Drops.
Hall Brothers, Whitefield, Manchester England.	Hall's Cherry Cough Drops.
Hoffman-LaRoche, Inc., Nutley, N.J. 07110.	Theporin, Phenindamine.
The Holford Co., Minneapolis, Minn. 55403	Holford's Famous Inhaler, Indian Chief Inhaler.
Ives Laboratories, Inc., New York, N.Y. 10017.	Cerose, Cerose Compound Cerose-DM, Cetro-Cerose.
Johnson & Johnson, New Brunswick, N.J. 08903.	Sine-Aid.
Key Pharmaceuticals, Inc., Miami, Fla. 33169.	Key Tusscapine.
Knoll Pharmaceutical Co., Whippany, N.J. 07981.	Verequad Suspension, Verequad Tablets.
LaMay's Asthma Eze, Inc., Kalaska, Mich. 49646.	Asthma Eze.
Luden's, Inc., Reading, Pa. 19601	Luden's Honey Lemon Cough Drops, Luden's Honey Licorice Cough Drops, Luden's Menthol Cough Drops, Luden's Menthol Eucalyptus Cough Drops, Luden's Wild Cherry Cough Drops.
Menley & James Laboratories, Philadelphia, Pa. 19101.	Contac.
The Metholatum Co., Inc., Buffalo, N.Y. 14213.	Mentholatum Ointment.
Merck and Co., Inc., Rahway, N.J. 07065	Nectadon.
Merck Sharp & Dohme, West Point, Pa. 19486.	Propadrine Capsules 25 mg, Propadrine Capsules 50 mg, Propadrine Elixir.
Miles Laboratories, Inc., Elkhart, Ind. 46514.	Alka-Seltzer Plus Cold Tablets.
Monsanto Co., St. Louis, Mo. 63166	Methapyrilene Fumarate, Methapyrilene Hydrochloride.
McNeil Laboratories, Inc., Fort Washington, Pa. 19034.	Co-Tylenol Cold Formula.

Mitchum-Thayer, Inc., New York, N.Y. 10020	Arrestin Extra Strength Cough Medicine with D-Methorphan, Asthma-Nefrin Solution "A" Inhalant, AsthmaNefrin Automatic Aerosol Mist, AsthmaNefrin Capsules, Liquiprin Nighttime Cold Medicine for Children.
Norwich Products, Norwich, N.Y. 13815	Norwich Baby Cough Syrup, Norwich Terpin Hydrate and Dextromethorphan Hydrobromide Elixir N.F., Quadrin Decongestive Tablets.
Parke-Davis & Co., Detroit, Mich. 48232	Benylin Cough Syrup, Benadryl.
S. B. Penick & Co., New York, N.Y. 10007	Glyceryl Guaiacolate.
Pfipharmecs Pfizer Pharmaceuticals, New York, N.Y. 10017.	Toclase Cough Syrup, Toclase Cough Tablets.
Pharmacraft, Rochester, N.Y. 14603	Allerest Allergy Tablets, Allerest Nasal Spray, Allerest Time Capsules, Children's Allerest Allergy Tablets, Sinarest.
Plough, Inc., Memphis, Tenn. 38101	St. Joseph Cough Syrup for Children.
Reid-Provident Laboratories, Inc., Atlanta, Ga. 30308.	Coton Syrup, Histalet-DM, Reidacol, Tusstrol, Tusstrol-DM.
A. H. Robins Co., Richmond, Va. 23220	Dimetane Elixir, Dimetane Tablets, Robitussets Troches, Robitussin, Robitussin-DM Cough Calmers, Robitussin-DM, Robitussin-PE Decongestant Expectorant.
Roerig, New York, N.Y. 10017	Coryban-D Cold Capsules, Coryban-D Cough Syrup, Coryban-D Nasal Spray.
Sandoz Pharmaceuticals, E. Hanover, N.J. 07936.	Flogesic.
Sauter Labs., Inc., Nutley, N.J. 07110	Children's Romilar Cough Syrup, Romilar CF Capsules, Romilar CF Syrup, Romilar CF 8-Hour Cough Formula, Romilar Chewable Cough Tablets for Children, Romilar Cough and Cold Capsules, Romilar Cough Discs, Romilar Expectorant, Romilar Hydrobromide Tablets, Romilar Syrup, Romilar III Cough Syrup with Expellin.
G. D. Searle & Co., Chicago, Ill. 60680	Amodrine.
Schering Corp., Bloomfield, N.J. 07003	Afrin Decongestant Nasal Spray, Afrin Decongestant Nose Drops, Chlor-Trimeton Antihistamine Syrup, Chlor-Trimeton Antihistamine Tablets, Coricidin "D" Tablets, Children's Coricidin Demilets Tablets, Children's Coricidin Medilets, Coricidin.
R. Schiffmann Co., Los Angeles, Calif. 90031	Asthmador.
Smith, Kline, & French Laboratories, Philadelphia, Pa. 19101.	Benzedrex Inhaler, Ornacol Cough and Cold Capsules, Ornacol Cough and Cold Liquid, Ornex, Toryn Syrup, Toryn Tablets.
E. R. Squibb & Sons, Inc., New Brunswick, N.J. 08903.	Spec-T Anesthetic Lozenges, Spec-T Sore Throat Decongestant Lozenges, Spec-T Sore Throat Spray, Spec-T Sore Throat Cough Suppressant Lozenges.
Sterling Products International, New York, N.Y. 10016.	Breacol with Prylon.
Templetons, Inc., Buffalo, N.Y. 14223	Raz-Mah Greys Capsules.
Henry Thayer Co., Cambridge, Mass. 02138	Thayers Slippery Elm Throat Lozenges, Thayers Slippery Elm Throat Lozenges (Wild Cherry).
Thayer Labs, Inc., Cambridge, Mass. 02138	AsthmaNefrin Syrup.
The Upjohn Co., Kalamazoo, Mich. 49001	Cheracol Cough Syrup, Cheracol D Cough Syrup, Cidicol Syrup, Elixir Terpin Hydrate and Codeine N.F., Elixir Terpin Hydrate and Codeine Sulfate, Emeracol Cough Syrup, Hydriodic Acid Cough Syrup, Aromatic Iodized Lime Expectorant Tablets, Orthoxicol Cough Syrup, Pyrroxate Capsules, Pyrroxate Tablets, Special Formula No. 2 Analgesic Antipyretic Tablets.
Vick Chemical Co., New York, N.Y. 10017	Vicks NyQuil Nighttime Colds Medicine, Vicks Cough Silencers, Vicks Cough Syrup, Vicks Formula 44 Cough Discs, Vicks Formula 44 Cough Mixture, Vicks Formula 44-D Cough Mixture, Vicks Inhaler, Vicks Medicated Cough Drops (Blue Mint), Vicks Medicated Cough Drops (Menthol-Eucalyptus), Vicks Medicated Cough Drops (Regular), Vicks Medicated Cough Drops (True Lemon), Vicks Medicated Cough Drops (Wild Cherry), Vicks Sinex Decongestant Nasal Spray, Vicks Vaporub, Victors Menthol-Eucalyptus Dual Action Cough Drops and Victors Menthol-Eucalyptus Dual Action Cough Drops (Cherry), Vicks Vaporub, Vicks Vaposteam, Oil of Turpentine, Doxylamine Succinate.

Warner-Chilcott Laboratories, Morris Plains, N.J. 07950.	Tedral Tablets, Tedral Anti-H Tablets, Tedral Pediatric Suspension.
Warner-Lambert Co., Morris Plains, N.J. 07950.	Listerine Big 4 Cough Formula, Hall's Mentho-Lyptus Cough Tablets, Listerine Antiseptic, Listerine Antiseptic Throat Lozenges (lemon-mint), Listerine Antiseptic Throat Lozenges (orange), Listerine Antiseptic Throat Lozenges (regular), Listerine Cold Tablet, Listerine Cough Control Lozenges, Smith Brothers Medicated Cough Drops (black licorice), Smith Brothers Medicated Cough Drops with Benzocaine (minted menthol), Smith Brothers Medicated Cough Drops (Wild Cherry), Super Anahist Decongestant Tablets, Super Anahist Decongestant Nasal Spray.
Whitehall Laboratories, Inc., New York, N.Y. 10017.	Bronitin Tablets, Bronitin Mist, Clear & Dry Sinus Clearant Tablets, Dondril Anticough Tablets, Dristan Decongestant Tablets, Dristan Capsules, Dristan Nasal Mist, Dristan Decongestant Vapor Nasal Spray, Primatene M Formula Tablets, Primatene Mist, Primatene P Formula Tablets, Dristan Decongestant Cough Formula.
Winthrop Laboratories, New York, N.Y. 10016.	Neo-Synephrine Compound Decongestant Cold Tablets, Neo-Synephrine HCl Decongestant Elixir, Neo-Synephrine HCl Jelly, Neo-Synephrine Nasal Spray ¼ percent, Neo-Synephrine Nasal Spray ½ percent, Neo-Synephrine Decongestant Nose Drops ⅛ percent, Neo-Synephrine Decongestant Nose Drops ¼ percent, Neo-Synephrine Decongestant Nose Drops ½ percent, Neo-Synephrine Decongestant Nose Drops 1 percent, NTZ Nasal Spray, NTZ Decongestant Nose Drops, Synephricol Antihistaminic Cough Syrup.
Winthrop Products, Inc., New York, N.Y. 10016.	NRT Antihistaminic Decongestant, NRT Nasal Spray, Asafen Tablets, Deka Expectorant Cough Syrup, NTR Decongestant Antihistaminic, NTR Nasal Spray, Recindal, Synephricol Cold Tablets, Neosynephrine Intranasal Drops ¼ percent, Neosynephrine Intranasal Drops 1 percent.
Wyeth Laboratories, Philadelphia, Pa. 19101.	Phenergan.

In addition, the following firms or groups made related submissions:

Firm	*Submissions*
Bristol-Myers Products, New York, N.Y. 10022.	Phenylephrine hydrochloride, Phenylpropanolamine.
Chattem Drug & Chemical Co., Chattanooga, Tenn. 37409.	Theophylline sodium glycinate.
Lilly Research Laboratories, Indianapolis, Ind. 46206.	Methapyrilene hydrochloride.
Miles Laboratories, Inc., Elkhart, Ind. 46514.	Phenylpropanolamine salts.
Parke Davis & Co., Detroit, Mich. 48232.	Diphenhydramine and pseudoephedrine.
A. H. Robins, Richmond, Va. 23220.	Glyceryl guaiacolate.
Smith, Kline & French Laboratories, Philadelphia, Pa. 19101.	Chlorpheniramine, Brompheniramine maleate, Phenylpropanolamine, propylhexedrine, caramiphen edisylate.
Linda Taliaferro, Austin, Tex. 78712.	Stramonium-belladonna.
Vick Chemical Co., New York, N.Y. 10017.	Topical ephedrine, doxylamine succinate, xylometazoline hydrochloride.
Vick Division Research, Mount Vernon, N.Y. 10553.	Alcohol.
Whitehall Laboratories, Inc., New York, N.Y. 10017.	Oral phenylephrine, and oral phenindamine.
Wyeth Laboratories, Inc., Philadelphia, Pa. 19101.	Promethazine hydrochloride.

B. LABELED INGREDIENTS CONTAINED IN MARKETED PRODUCTS SUBMITTED TO THE PANEL

Acetaminophen (*N*-acetyl-*p*-aminophenol)
Acetic acid
N-acetyl-*p*-aminophenol (acetaminophen)
Alcohol
Alkyl dimethyl benzylammonium chloride (benzalkonium chloride)
Aloin
Aluminum hydroxide-magnesium carbonate co-dried gel
Aminophylline
Ammonium chloride
Anethole
Anise
Antimony potassium tartrate
Ascorbic acid (vitamin C)
Aspirin
Atropine sulfate
Banana arome
Beechwood creosote
Belladonna
Belladonna alkaloids
Benzalkonium chloride (alkyl dimethyl benzylammonium chloride)
Benzocaine
Benzyl alcohol
Benzaldehyde
Blood root
Boric acid
Bornyl acetate
Brompheniramine maleate
Bryonia tincture
Caffeine
Calcium carbaspirin
Calcium iodide anhydrous (iodides)
Camphor
Capsicum
Caramel
Caramiphen edisylate (caramiphen ethanedisulfonate)
Caramiphen ethanedisulfonate (caramiphen edisylate)
Carbetapentane citrate
Cascara
Cedar leaf oil
Cedar, natural
Cetalkonium chloride
Cetylpyridinium chloride
Cherry flavoring
Cherry nut flavoring
Chlorobutanol
Chloroform
Chlorpheniramine maleate
Citric acid
Citric acid (hydrate)
Cocillana
Cod liver oil
Codeine
Codeine alkaloid
Codeine phosphate
Codeine sulfate
Compound white pine syrup
1-Desoxyephedrine
Dextromethorphan
Dextromethorphan hydrobromide
Dextrose
Dioctyl sodium sulfosuccinate
Diphenhydramine hydrochloride
Dipropylene glycol
Disodium edetate
Doxylamine succinate
Drosera tincture
Elm bark
Ephedrine
Ephedrine hydrochloride
Ephedrine sulfate
Epinephrine
Epinephrine bitartrate
Epinephrine hydrochloride (racemic)
Eriodictyon fluid extract (yerba santa)
Ethylmorphine hydrochloride
Eucalyptol
Eucalyptus oil
Euphorbia pilulifera
Exract white pine compound
F. E. Horehound
Fluidextract ipecac (ipecac fluidextract)
Glycerin
Glyceryl guaiacolate
Glycyrrhiza (licorice)
Grape flavoring
Grindelia
Gum arabic
Hexylresorcinol
Honey
Hydriodic acid (iodides)
Hydrocodone bitartrate
Hyoscyamine sulfate
Iodides (calcium iodide anhydrous, hydriodic acid syrup, iodized lime, potassium iodide)
Iodized lime (iodides)
Ipecac
Ipecac fluidextract (fluidextract ipecac)
Lemon oil
Licorice (glycyrrhiza)
Lobelia
Lobelium
Menthol/peppermint oil
Methapyrilene fumarate
Methapyrilene hydrochloride
Methoxyphenamine hydrochloride
Methylcellulose
Methylparaben

Methyl salicylate
Monocalcium phosphate
Mustard oil
Myristica oil
Naphazoline hydrochloride
Noscapine
Noscapine hydrochloride
Oil of pine
Oleyl alcohol
Oxymetazoline hydrochloride
Peppermint oil/menthol
Petrolatum base
Phenacetin
Phenindamine tartrate
Pheniramine maleate
Phenobarbital
Phenylephrine bitartrate
Phenylephrine hydrochloride
Phenylmercuric acetate
Phenylpropanolamine hydrochloride
Phenylpropanolamine bitartrate
Phenylpropanolamine maleate
Phenyltoloxamine citrate
Pineapple flavoring
Pine tar
Podophyllum resin
Potassium guaiacolsulfonate
Potassium nitrate
Promethazine hydrochloride
Propylhexedrine
Propylparaben
Pseudoephedrine sulfate
Pyrilamine maleate
Quinine sulfate
Racemic epinephrine hydrochloride
Racephedrine hydrochloride
Rumex
Salicylamide
Saline phosphate buffer solution
Scopolamine hydrobromide
Sodium bicarbonate
Sodium bisulfite
Sodium citrate
Spirits of turpentine (turpentine oil)
Squill extract
Sticta pulmonaria
Stramonium
Sucrose
Sugar
Sugar base
Syrup base
Terpin hydrate
Thenyldiamine hydrochloride
Theophylline
Theophylline anhydrous
Theophylline calcium salicylate
Thimerosal
Thonzonium bromide
Thonzylamine hydrochloride
Thymol
Tincture of benzoin
Tolu
Tolu balsam
Tolu balsam tincture
Triethylene glycol
Vegetable stearate
Vitamin C (ascorbic acid)
White pine
Wild cherry
Wild cherry fluid extract
Yerba santa (eriodictyon fluid extract)
Xylometazoline hydrochloride

Ingredients reviewed by the Panel in addition to the submitted data:

Ipecac syrup
Potassium iodide (iodides)
Theophylline sodium glycinate

C. CLASSIFICATION OF INGREDIENTS

1. Active ingredients. The Panel has classified the following ingredients submitted to the Panel into groups identified below:

ANTITUSSIVES

Beachwood creosote
Camphor
Caramiphen edisylate (caramiphen ethanedisulfonate)
Caramiphen ethanedisulfonate (caramiphen edisylate)
Carbetapentane citrate
Cod liver oil
Codeine
Codeine alkaloid
Codeine phosphate
Codeine sulfate
Dextromethorphan
Dextromethorphan hydrobromide
Diphenhydramine hydrochloride
Elm bark
Ethylmorphine hydrochloride
Eucalyptol/eucalyptus oil
Horehound
Horehound (horehound fluid extract)
Hydrocodone bitartrate (dihydrocodeinone)
Menthol/peppermint oil
Noscapine
Noscapine hydrochloride
Thymol
Turpentine oil (spirits of turpentine)

EXPECTORANTS

Ammonium chloride
Antimony potassium tartrate
Beechwood creosote
Camphor
Chloroform
Compound benzoin tincture
Compound white pine syrup
Eucalyptol/eucalyptus oil
Extract white pine compound
Glyceryl guaiacolate
Iodides (calcium iodide anhydrous, hydriodic acid syrup, iodized lime, potassium iodide)
Ipecac fluidextract
Ipecac syrup
Menthol/peppermint oil
Pine tar
Potassium guaiacolsulfonate
Sodium citrate
Squill
Squill extract
Syrup of pine tar
Terpin hydrate
Terpin hydrate elixir
Tincture of benzoin
Tolu
Tolu balsam
Tolu balsam tincture
Turpentine oil (spirits of turpentine)
White pine

BRONCHODILATORS

SYMPATHOMIMETIC AMINES

Belladonna alkaloids
Ephedrine
Ephedrine hydrochloride
Ephedrine sulfate
Epinephrine
Epinephrine bitartrate
Epinephrine hydrochloride (racemic)
Methoxyphenamine hydrochloride
Pseudoephedrine hydrochloride
Pseudoephedrine sulfate
Racephedrine hydrochloride

THEOPHYLLINES

Aminophylline
Theophylline anhydrous
Theophylline calcium salicylate
Theophylline sodium glycinate

MISCELLANEOUS

Euphorbia pilulifera

ANTICHOLINERGICS

Atropine sulfate
Belladonna
Belladonna alkaloids
Hyoscyamine sulfate
Scopolamine hydrobromide
Stramonium

ANTIHISTAMINES

Brompheniramine maleate
Chlorpheniramine maleate
Diphenhydramine hydrochloride
Doxylamine succinate
Methapyrilene fumarate
Methapyrilene hydrochloride
Phenindamine tartrate
Pheniramine maleate
Phenyltoloxamine citrate
Promethazine hydrochloride
Pyrilamine maleate
Thenyldiamine hydrochloride
Thonzylamine hydrochloride

NASAL DECONGESTANTS

Beechwood creosote
Bornyl acetate
Camphor
Cedar leaf oil
1-Desoxyephedrine
Ephedrine
Ephedrine hydrochloride
Ephedrine sulfate
Eucalyptol/eucalyptus oil
Menthol/peppermint oil
Mustard oil (allylisothiocyanate)
Naphazoline hydrochloride
Oxymetazoline hydrochloride
Phenylephrine hydrochloride
Phenylpropanolamine hydrochloride
Phenylpropanolamine bitartrate
Phenylpropanolamine maleate
Propylhexedrine
Pseudoephedrine hydrochloride
Pseudoephedrine sulfate
Racephedrine hydrochloride
Thenyldiamine hydrochloride
Thymol
Turpentine oil (spirits of turpentine)
Xylometazoline hydrochloride

2. Miscellaneous labeled ingredients:

Antihistamines with sleep-aid claims
Ascorbic acid (vitamin C)
Caffeine
Phenobarbital
Vitamins

3. Ingredients submitted to the Panel and classified as inactive and/or pharmaceutical necessary ingredients:

Acetic acid
Alcohol
Alkyl dimethyl benzylammonium chloride (benzalkonium chloride)
Aluminum hydroxide—magnesium carbonate (co-dried gel)
Anethole
Anise
Banana arome
Benzaldehyde
Benzalkonium chloride (alkyl dimethyl benzylammonium chloride)
Blood root
Bryonia tincture
Caramel
Cedar, natural
Cetalkonium chloride
Cetylpyridinium chloride
Cherry flavoring
Cherry nut flavoring
Chlorobutanol
Chloroform (0.4% maximum)
Citric acid
Citric acid (hydrate)
Cocillana
Dextrose
Dipropylene glycol
Disodium edetate
Drosera tincture
Eriodictyon fluidextract (yerba santa)
Glycerin
Glycyrrhiza (licorice)
Grape flavoring
Grindelia
Gum arabic

Honey
Lemon oil
Licorice (glycyrrhiza)
Lobelia
Lobelium
Methyl cellulose
Methylparaben
Monocalcium phosphate
Myristica oil
Oleyl alcohol
Petrolatum base
Phenylmercuric acetate
Pineapple flavoring
Potassium nitrate
Propylparaben
Rumex
Saline phosphate buffer solution
Sodium bisulfite
Sticta pulmonaria
Sucrose
Sugar
Sugar base
Syrup base
Thimerosol
Thonzonium bromide
Triethylene glycol
Vegetable stearate
Wild cherry
Wild cherry fluidextract
Yerba santa (eriodictyon fluidextract)

4. Ingredients submitted to the Panel and deferred to other OTC advisory review panels.

a. Ingredients deferred to the Advisory Review Panel on OTC internal analgesic including antirheumatic drug products:

(1) Acetaminophen (*N*-acetyl-*p*-aminophenol)
(2) *N*-acetyl-*p*-aminophenol (acetaminophen)
(3) Aspirin
(4) Calcium carbaspirin
(5) Phenacetin
(6) Quinine sulfate
(7) Salicylamide

b. Ingredients deferred to the Advisory Review Panel on OTC laxative, antidiarrheal, emetic and antiemetic drug products:

(1) Aloin
(2) Cascara
(3) Dioctyl sodium sulfosuccinate
(4) Podophyllum resin

c. Ingredients deferred to the Advisory Review Panel on OTC topical analgesic, antirheumatic, otic, burn, and sunburn treatment and prevention drug products:

(1) Benzocaine
(2) Benzyl alcohol
(3) Boric acid
(4) Capsicum
(5) Methyl salicylate

d. Ingredients deferred to the Advisory Review Panel on OTC oral cavity drug products:

(1) Hexylresorcinol
(2) Methyl salicylate

e. Ingredient deferred to the Advisory Review Panel on antacid drug products:

(1) Sodium bicarbonate

II. General Statements and Recommendations

A. General Comment

The OTC cold, cough, allergy, bronchodilator and antiasthematic Panel was charged with the review and the evaluation of safety and effectiveness data on cold, cough, allergy, bronchodilator, and antiasthmatic ingredients and combinations thereof, the adequacy of their labeling, and to advise the Commissioner of Food and Drugs on the promulgation of monographs establishing conditions under which these over-the-counter (OTC) drug products are generally recognized as safe and effective and not misbranded. The Panel also served as a forum for the exchange of views regarding the prescription or nonprescription status of these various active ingredients and combinations thereof. Panel members were expected to call upon their own expert knowledge and experience in carrying out each element of this charge. Specifically the Panel was charged with the following:

1. Review and evaluation of all data made available to the panel members concerning the safety and effectiveness of cold, cough, allergy, bronchodilator and antiasthmatic treatment and prevention agents, and combinations thereof, utilized in these OTC drug products.

2. Advising the Food and Drug Administration as to the adequacy of the labeling of such cold, cough, allergy, bronchodilator and antiasthmatic treatment and prevention drug products and to make recommendations as to the contents of future labeling of such products.

3. Making recommendations to the Food and Drug Administration regarding those ingredients, their amounts, and combinations thereof, which, based upon the available data, could be considered safe and effective for the above stated uses. These recommendations must be in keeping with agency stated definitions of the terms "safe" and "effective" and in keeping with the agency OTC drug combination policy (21 CFR 330.10(a)(4)(iv)).

4. Making recommendations to the Food and Drug Administration regarding those ingredients, their amounts, and combinations thereof, which based upon the available data, are not considered as safe and effective for the above stated uses. The same criteria must apply as in the determinations of those ingredients which are found to be safe and effective.

5. Advising the Food and Drug Administration regarding those ingredients which in their judgment are likely to be safe and effective, but for which more data are needed. In such cases the Panel was requested to give some guidance as to what type of studies and the maximum time period they feel would be adequate to produce such information for future consideration by the Food and Drug Administration.

6. Advising the Food and Drug Administration on the promulgation of a monograph or monographs establishing conditions under which these OTC drug products are generally recognized as safe and effective and not misbranded. This information is submitted in the form of a written report by the Panel containing the following basic recommendations:

a. Listing of the acceptable active ingredients, singly or combinations thereof.

b. Acceptable dosage ranges of these active ingredients and their combinations.

c. A statement of the acceptable indications for use.

d. Recommended labeling guidelines—warnings, precautions, contraindications, directions for use.

B. Diseases and Related Symptoms Relieved by OTC Cold, Cough, Bronchodilator and Antiasthmatic Products

The Panel makes the following statements and recommendations concerning the symptoms related to the use of antitussives, expectorants, bronchodilators, anticholinergics, antihistamines and nasal decongestants. The symptoms which these drugs may be expected to relieve are those occurring in certain allergic states such as hay fever, asthma, and symptoms in the nose, eyes, sinuses and throat caused by the common cold and other mild respiratory infections. It must be kept in mind that the ingredients and combinations reviewed are not intended to cure but are OTC drugs to provide symptomatic relief.

The Panel has prepared the following table which lists symptoms and the acceptable corresponding pharmacologic groups of drugs for the treatment of these symptoms:

Symptom	*Pharmacologic group*
1. Bronchospasm or asthma	Bronchodilators (sympathomimetic amines, theophyllines)—with the Category I labeling indications recommended by the Panel. (See pt. V. par. B.1. below—Labeling.)
2. Cough	Antitussives—with the Category I labeling indications recommended by the Panel. (See pt. III. par. B.1. below—Labeling.)
	Expectorants—with the Category I labeling indications recommended by the Panel. (See pt. IV. par. B.1. below—Labeling.).
3. Runny nose	Anticholinergics—with the Category I labeling indications recommended by the Panel. (See pt. VI. par. B.1. below—Labeling.)
4. Nasal congestion	Nasal decongestants—with the Category I labeling indications recommended by the Panel. (See pt. VIII. par. B.1. below—Labeling.)
5. Sinus congestion	Do.
	Analgesics—with the Category I labeling indications recommended by the OTC Internal Analgesic Panel.
6. Sneezing, watery eyes, and itchy eyes	Antihistamines—with the Category I labeling indications recommended by the Panel. (See pt. VII. par. B.1. below—Labeling.)
7. Sore throat	Analgesics—with the Category I labeling indications recommended by the OTC Internal Analgesic Panel.
	Local anesthetics—with the Category I labeling indications recommended by the OTC Oral Cavity Panel.
8. Generalized aching	Analgesics—with the Category I labeling indications recommended by the OTC Internal Analgesic Panel.
9. Fever	Antipyretics—with the Category I labeling indications recommended by the OTC Internal Analgesic Panel.

1. *Allergy.* Allergy is a complex of symptoms which arises under circumstances when a person who has acquired a hypersensitivity to a substance encounters that substance. Although one may be born with a tendency to become allergic, one must be exposed to a substance for weeks, months or years before one actually becomes allergic to it. Probably about 15 percent or more of the population becomes significantly allergic. Substances to which people ordinarily become allergic are pollens, mold spores, animal dander and certain dusts and sprays in the home and in industry. These are airborne and are inhaled. One may also become allergic to certain foods and drugs and to substances coming in contact with the skin such as drugs and poison ivy (poison oak). Substances to which people become allergic are called allergens. In our highly industrial and technological society we are increasingly exposed to allergens never encountered by our forebears; for this reason, the number of persons with allergies is rising and may continue to rise.

The allergic symptoms with which the Panel is concerned are nasal (sneezing, watery or mucous discharge, itching and obstruction), and bronchial (cough, bronchospasm and expectoration). Another manifestation of allergy is itchy and watery eyes. Allergy of this type belongs to a subgroup of the so-called "immune" class of disease termed "atopy." In this class of disease an antibody mediates the reaction. The antibody belongs to the IgE class of immunoglobulins which has the peculiarity of attaching itself to a certain type of cell (mast cells in the tissues and basophils in the blood). With the arrival of the allergen, union between the allergen and the antibody attached to these cells occurs and leads to the release of substances which in turn cause the symptoms we call "allergic." One of the substances released, and perhaps the principal one, is histamine. The antihistaminic drugs block the action of histamine.

Identification and elimination of the offending substance (allergen) are the measures of choice. However, these are often impossible to achieve. The proper use of OTC products containing antihistamines, sympathomimetics, or theophyllines may provide relief of allergy symptoms. Although OTC drugs are often adequate for relief, the allergic reaction may be so intense that OTC drugs are not adequate and other measures, such as epinephrine by injection, and corticosteroids, requiring the supervision of a physician are needed. In the case of allergy to pollens and some other inhaled allergens, symptoms can be lessened or eliminated under medical supervision by a course of injections of suitably prepared allergenic extract.

REFERENCES

(1) Sheldon, J. M., R. G. Lovell and K. P. Mathews, "A Manual of Clinical Allergy," 2d Ed., W. B. Saunders Co., Philadelphia, 1967.

(2) Patterson, R., "Allergic Diseases: Diagnosis and Management," The J. B. Lippincott Co., Philadelphia, 1972.

2. *Asthma and other respiratory diseases and the use of bronchodilators.* Asthma is a disease in which there is widespread narrowing of the airways due to airway wall muscle spasm which occurs in response to various stimuli. Among the stimuli which may lead to asthma is the inhalation of substances such as pollens and animal danders in people who are allergic to these substances. This reaction causes partial obstruction to air flow and shortness of breath. The spasm causing narrowing of the air tubes may subside either spontaneously or as a result of therapy. Airway narrowing occurs also where there is widespread bronchial infection such as in acute or chronic bronchitis, in pulmonary emphysema where there is destruction of the lung tissue, and in pulmonary congestion from failure of the left side of the heart. Asthma is a difficult disease condition for the layman to diagnose and even physicians have difficulty in distinguishing asthma from the above other conditions which cause airway narrowing. Therefore, it is very important that the diagnosis of asthma first be established by a physician before the use of OTC bronchodilator preparations.

Medications which relax the airway muscle spasm and relieve the shortness of breath of asthma are called bronchodilators. Usually these drugs are given by mouth as a tablet or liquid, or they may be inhaled as a spray from a suitable dispenser. The response of mild or even moderate asthma to these drugs is often quick and there is effective relief from shortness of breath. The Panel believes that, when taken as directed, the drugs are safe for OTC use, but undesirable effects can occur. These adverse effects are mainly exhibited as increased rate and force of the heart beat, rise in blood pressure, nervousness and sleeplessness, and nausea or vomiting.

Asthma is a very common disease and it is reasonable to have bronchodilators available on a nonprescription basis so that in mild cases relief may be obtained quickly without the possible delays of obtaining a physician's prescription. However, it is very important that the diagnosis of asthma first be established by a physician as some of the other conditions which resemble asthma, such as pulmonary congestion from failure of the left side of the heart, should not be treated by certain types of bronchodilators. Even the patient with true asthma should be warned that if a bronchodilator does not cause excellent and rapid relief, he should call his physician. The reason he should call his physician is that in a severe and worsening attack of asthma, slight relief may be given by these bronchodilators and this may give a false sense of security. The patient may then postpone seeking medical help or going to a hospital until his disease has reached life-threatening severity. Therefore, labeling of these preparations should be very precise in that the patient should be instructed to seek medical assistance immediately if relief of his symptoms does not occur within a short time of us-

ing the bronchodilator preparation. In the use of epinephrine aerosol, relief should occur within 20 minutes; in the use of ephedrine, methoxyphenamine tablets and tablets of theophylline and its salts, relief should occur within 1 hour.

REFERENCES

(1) Harris, H. W. et al., "Chronic Bronchitis, Asthma and Pulmonary Emphysema. A statement by the Committee on Diagnostic Standards for Nontuberculous Respiratory Disease, American Thoracic Society," *American Review of Respiratory Diseases*, 85:762–768, 1962.

3. *The "common cold" (cold).* The "common cold" (cold) is a self-limited respiratory infection caused by one or more viruses. A cold is rarely serious and is readily transmitted. Throughout this document, the Panel has used the term "common cold" which the Panel considers synonymous with the term "cold."

A "common cold" often begins quite abruptly with soreness or discomfort in the pharynx, sneezing, watery nasal discharge, followed by nasal congestion. The discharge may subsequently become mucoid or purulent. After the first day or two the eyes may become suffused and the voice husky. The nasal congestion intensifies and the sense of smell and taste is often suppressed or absent. Extension into the sinuses may occur as described in the rhinitis statement. Lethargy, some aches and pains and slight fever may be present. The course is variable and may extend for 7 to 14 days. Cough may occur, especially in the later stages.

Early in its course, the cold is indistinguishable from the early stages of measles, rubella, chickenpox, pertussis, cerebrospinal fever, influenza and atypical pneumonia. The cold also closely simulates allergic rhinitis. The physician's main role in the cold is to exclude more serious illness.

There is no generally accepted treatment that can prevent, cure or shorten the course of the "common cold." Treatments which are available only relieve symptoms. Immunity is apparently of short duration since many individuals have one to three colds each year.

4. *Cough.* A cough is the rapid expulsion of air at high velocity from the respiratory airway producing a noise of varying pitch and intensity. Impulses that initiate the cough reflex may arise from many areas within and outside the respiratory tract.

Normally, coughing is produced by stimulation of the sensory endings of the glossopharyngeal and vagus nerves within the mucous membranes of the respiratory tract. This stimulation can be initiated by infection, chemical irritation, the presence of retained secretions, or foreign material blocking the breathing passages. Localized narrowing of the air tubes may play an important role in stimulation of the cough reflex. Cough can also occur from stimulation outside the respiratory tract. For example, if the external ear is tickled, a cough is produced. Cough can be under considerable voluntary control and therefore can be self-suppressed to a degree. Likewise, an individual can initiate a cough at will. Cough occurs in healthy individuals as a mechanism for clearing the airway of any obstructing mucus or inhaled foreign material.

Medications which suppress the act of coughing by reducing the number of coughs and/or the intensity of coughing are known as antitussive drugs. These preparations are administered by mouth in the form of tablets, syrups, elixirs and lozenges, and by inhalation in the form of rubs and vaporizer additives, and when used as directed provide relief from annoying cough. These drugs are generally safe at the dosages recommended for OTC use. However, antitussives derived from narcotics, such as codeine and hydrocodone, commonly cause constipation as a side effect.

The cough is a protective, physiologic reflex occurring in healthy as well as diseased individuals. It is frequently the presenting symptom in a wide variety of pathologic states, ranging from a mild, self-limiting illness to a serious and even fatal disease. In certain disease states such as asthma, chronic bronchitis and cystic fibrosis, the cough reflex is essential in maintaining an open airway by clearing the respiratory passages of excessive secretions. Because of its importance in preserving the function of the lung, by maintaining an open airway, the cough reflex should not be suppressed indiscriminately.

The irritative cough associated with a self-limiting respiratory tract infection is usually viral in nature or follows the inhalation of irritant gases or dusts, and can readily be recognized and serves no useful function. These conditions are usually associated with a dry, hacking, nonproductive cough in which no sputum is expectorated and lends itself to rational self-medication with OTC preparations. On the other hand, the loose, productive type of cough frequently associated with asthma and bronchitis indicates the presence of retained bronchial secretions which could lead to increasing disability if suppressed; and therefore, should not be treated with an antitussive drug. Any cough which persists for longer than 1 week should be investigated by a physician to exclude the presence of an underlying, potentially serious, respiratory disease.

5. *Symptoms of sinus congestion.* Paranasal sinuses are mucous membrane-lined air cavities in the bony structure of the skull which are continuous with the nasal cavity. Impaired sinus drainage due to nasal congestion, e.g., rhinitis of upper respiratory infection or nasal allergy, may result in sinus inflammation (sinusitis) with associated headache and facial pain or tenderness in the region of the affected sinus(es).

Self-medication with an oral or topical nasal decongestant may aid in resolving the problem by diminishing the nasal obstruction which impairs sinus drainage. An orally administered analgesic, e.g., aspirin, acetaminophen, should provide symptomatic relief from headache and pain associated with the sinus congestion. If symptoms persist, intensify and/or are accompanied by fever, a physician should be consulted.

6. *Rhinitis (allergic rhinitis, vasomotor rhinitis).* a. *Allergic rhinitis.* Allergic rhinitis is caused by allergy to airborne allergens including pollens, animal danders, molds and house dust as described elsewhere in this document. (See part II. paragraph B.1. above—Allergy).

The symptoms of allergic rhinitis are sneezing, watery discharge from the nose, nasal stuffiness and obstruction and nasal itching. The eyes may also be involved in which case there is itching, tearing or redness. There may also be puffiness of the eyelids. Less frequently there is headache, itching of the throat and ears and there may be cough. A few patients feel listless or very tired and some describe themselves as feeling generally ill. Hay fever is the familiar example of allergic rhinitis which occurs in persons allergic to pollens.

In addition to rhinitis the paranasal sinuses are frequently involved. This may cause headache usually frontal in distribution or pain or discomfort in the area of the frontal, ethmoid, maxillary or antral sinuses in the front of the face surrounding the nose.

Sneezing may occur irregularly or in paroxysms, more commonly on awaking in the morning, or may be caused by such nonspecific factors as exposure to abrupt changes in temperature or inhalation of particulate matter.

The nasal discharge may be watery in nature, mucoid or purulent. When purulent, bacterial infection is usually assumed to be present. However, this feature is determined by the number of white cells present and not necessarily by the presence of infectious organisms. The nasal discharge of some patients with rhinitis contains such a large number of eosinophils that the discharge acquires a purulent appearance without evidence of infection.

Rhinitis is classically an allergic response to an inhaled allergen, be it pollen, mold or animal dander. However, rhinitis also occurs as the characteristic feature of infections such as the "common cold."

The diagnosis of allergic rhinitis its based on a history of characteristic symptoms as described above and the demonstration by skin testing that the injection of an aqueous extract prepared from the appropriate pollen or allergen will cause within 10 to 20 minutes local redness, a wheal and itching similar to the reaction to the bite of a mosquito. Examination of the nose characteristically but not invariably shows swelling of the internal membranes which are often pearly gray or reddened instead of pink, their normal color.

b. *Vasomotor rhinitis.* There also occurs a form of rhinitis the symptoms of which are not caused by any recognized allergic exposure. This form of rhinitis tends to occur throughout the year with little or no seasonal variation. The condition is usually called vasomotor rhinitis suggesting an abnormal reactivity of the

blood vessels in the nasal lining but in fact the reason for symptoms is unknown. The symptoms of vasomotor rhinitis are the same as those in allergic rhinitis. Skin tests are not helpful in diagnosis.

c. *Treatment of rhinitis symptoms.* The antihistamines are most effective in the treatment of mild allergic rhinitis (such as hay fever). They are less effective in vasomotor rhinitis. These drugs are discussed more completely later in this document. (See part VII. below—Antihistamines.) Nasal decongestants and anticholinergics have also been used in the management of the symptoms of rhinitis. The use of these drugs will be discussed more completely later in this document. (See part VI. below—Anticholinergics and part VIII. below—Nasal Decongestants.)

C. PRINCIPLES APPLICABLE TO COMBINATION PRODUCTS

1. *General combination policy.* Most cold, cough, allergy, bronchodilator and antiasthmatic (CCABA) products currently in the marketplace containing ingredients which the Panel reviewed are promoted or sold to relieve a number of different symptoms. For example, OTC products commonly used for the treatment of the symptoms of the "common cold" include ingredients intended to provide relief of two or more concomitant symptoms such as nasal congestion, running nose, coughing, watery eyes, headache, fever and muscular aches. These products contain more than one active ingredient in order to cover a spectrum of symptoms. Some of these OTC preparations contain ingredients not reviewed by the Panel, e.g., aspirin, which has been deferred to the Advisory Review Panel on OTC internal analgesic including antirheumatic drug products for evaluation of analgesic and antipyretic claims.

In order to clarify the place of combinations in the marketplace, the Panel applied the OTC Drug Review Regulation (21 CFR 330.10(a)(4)(iv)) which states:

> An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients and when the combination, when used under adequate direction for use, and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

The Panel concurs with the regulation and strongly believes that each active ingredient in a combination product must contribute to the claimed effects and that each active ingredient must be necessary for rational therapy of concurrent symptoms. It is the view of the Panel that it is irrational to use a combination product unless each of the contained active ingredients contributes to the effective treatment of at least one of the labeled symptoms for which the combination product is recommended.

The Panel is familiar with the arguments for combination products and at the same time recognizes the disadvantages of fixed-dosage combination products. One major disadvantage commonly expounded is the inability to permit individualized dosage of each active ingredient. The Panel agrees in principle with this argument. However, if the combination product contains only active ingredients at doses of demonstrated safety and effectiveness and all ingredients are necessary for treatment of symptoms, the Panel concludes that certain combinations may offer a convenient and rational approach for relief of concurrent symptoms.

The Panel refers to a recognized source of drug information which notes that cold remedy mixtures are widely used and enjoy a certain amount of acceptance by the medical profession and the laity (Ref. 1). It is the view of the Panel that certain combinations, as established by the Panel are acceptable and summarized below. (See part II. paragraph C.8.b. below—Criterion.) To support this view, the Panel refers to the conclusion in the above-referenced text (Ref. 1) which states "* * * a physician who chooses to prescribe a cold remedy must be certain that the mixture is composed of drugs with known effectiveness, that the ingredients are present in adequate therapeutic amounts, and that they are therapeutically rational for the type and severity of symptoms being treated."

The Panel has established specific criteria for the treatment of symptoms with combination products. Each Category I combination is currently limited to one active ingredient from any one pharmacologic group. The Panel has placed combinations of two active ingredients from the same pharmacologic group in Category III. Each active ingredient must be generally recognized as safe and effective when used alone for the labeled claim(s) and hence make a contribution to the claimed effect(s) of the combination. The acceptable pharmacologic groups included for treatment of symptoms as determined by the Panel differ sufficiently one from another to reduce the likelihood of a competitive or potentiating effect between agents. Therefore, the Panel has recommended only specific combinations be provided and limited to one active ingredient from any one pharmacologic group. The Panel concludes that products containing the combinations of ingredients provided for below are safe and effective. (See part II. paragraph C.8.b. below—Criterion.)

The Panel further concludes that such combinations of ingredients can provide rational concurrent therapy for a significant and existing target population that can benefit from such use. The Panel emphasizes that these combinations must contain adequate directions for use and include warnings against unsafe use. These combinations of ingredients must clearly indicate in their labeling that they are to be used only when the multiple symptoms are present concurrently. It would not be rational for a consumer having only one symptom to take a combination of ingredients intended for treatment of more than one symptom, or containing active ingredient(s) not required for relief of symptoms present in that individual.

2. *Limitation of ingredients in combination products.* The Panel concludes that, in general, the fewer the ingredients in an OTC product, the safer and more rational the therapy. The Panel has discussed the advantages of single ingredient products elsewhere in this document. (See part II. paragraph J. below—Advantages of Single Ingredient Products.) The Panel believes that the interests of the consumer are best served by exposing the user of OTC drugs to the smallest number of ingredients possible at the lowest possible dosage consistent with a satisfactory level of effectiveness. OTC drugs containing safe and effective single active ingredients are preferred to those having multiple active ingredients because with fewer ingredients there is a reduced risk of undesirable additive or synergistic effects.

Single ingredients are also preferred because the ratio in which components exist in a fixed combination may be unsuitable for some individuals. This is due in part to the great variability of reactions and side effects among these persons to the various drugs in the combination. It is also due in part to the inability of such persons to correlate certain side effects with the use of a particular drug when more than one drug is present in a combination. Both points are discussed more fully elsewhere in this document. (See part II. paragraph J. below—Advantages of Single Ingredient Products.)

The Panel believes that single active ingredient preparations should be available in the OTC market to allow the consumer the opportunity of selecting a single drug for a specific symptom or symptoms. As an example, a single active ingredient preparation containing only an antitussive should be available for treatment of cough. Likewise, a single active ingredient preparation containing only an antihistamine should be available for treatment of running nose, sneezing, and watery eyes. It is the Panel's opinion that presently the public has too little choice in selecting an appropriate drug treatment for such symptoms because of the current OTC market scarcity of single drug ingredient preparations.

In fact, of the 339 volumes received as submissions for review by the Panel, only 44 volumes contained data concerning 24 single active ingredients being marketed in 46 products. This represents 24 single active ingredients, out of a total of 152 active ingredients submitted by firms, as being present in marketed OTC CCABA products. The 46 products containing the single active ingredient represent a wide variety of dosage forms which include aerosols, liquids, tablets, syrups, drops, sprays, jellies and elixirs. The Panel has prepared the following table of the 24 single active ingredients marketed alone in CCABA products and submitted to the Panel for review:

MARKETED DRUG PRODUCTS CONTAINING A SINGLE ACTIVE INGREDIENT

Active ingredient	*Dosage form (number of products)*
Products for the relief of asthma:	
Epinephrine hydrochloride	Aerosols (5) and solutions (1).
Products for the relief of cough:	
Ammonium chloride	Drops (1).
Caramiphen ethanedisulfonate	Do.
Carbetapentane citrate	Syrups (1) and drops (1).
Cocillana	Drops (1).
Dextromethorphan	Syrups (2).
Menthol	Drops (2).
Noscapine	Syrups (2) and bulk chemicals—not a marketed drug product (1).
Products for relief of nasal congestion:	
Naphazoline hydrochloride	Drops (1) and sprays (1).
Oxymetazoline hydrochloride	Do.
Phenylephrine	Drops (1).
Phenylephrine hydrochloride	Sprays (2), jellies (1), and elixirs (1).
Phenylpropanolamine hydrochloride	Tablets (2) and liquids (1).
Xylometazoline hydrochloride	Drops (2) and sprays (2).
Products for use as antihistamines:	
Brompheniramine maleate	Tablets (1) and liquids (1).
Chlorpheniramine maleate	Tablets (1) and syrups (1).
Methapyrilene fumarate	Bulk chemicals—not a marketed drug product (1).
Methapyrilene hydrochloride	Bulk chemicals—not a marketed drug product (1).
Promethazine	Liquids (1).
Products for use as an expectorant:	
Glyceryl guaiacolate	Liquids (2).
Hydriodic acid	Liquids (1).
Iodized lime	Tablets (1).
Products for use in relief of sore throat:	
Benzocaine	Lozenges (1).
Hexylresorcinol	Lozenges (3).

The Panel concludes that in light of the numerous CCABA combination products on the market, there appears to be a shortage of single active ingredient products for the consumer to adequately and individually treat a specific symptom. This may or may not be representative of the marketplace but certainly indicates a paucity of single ingredient products. The Panel recommends that this situation be altered so that the public may make a more discriminating selection in the purchasing of OTC drugs. The Panel recognizes the consumer's prerogative for self-medication and believes that this can only be fully realized when single as well as combination products are more readily available.

The Panel is also aware of the inclusion of inactive, i.e., nontherapeutic, ingredients in CCABA preparations. These inactive ingredients are used for various purposes such as preservatives and flavors for specific product formulations. The Panel recognizes that some ingredients may be necessary for marketing purposes. However, the Panel recommends that the safety of inactive ingredients and the advisability of including them in drug products be reviewed by an appropriate body. The Panel further discusses inactive ingredients elsewhere in this document. (See part II. paragraph I. below—Inactive Ingredients.)

In summary, the Panel recommends that marketed products contain only those active and inactive ingredients that are essential to the product.

3. *Combining of active ingredients reviewed by the Panel from different pharmacologic groups.* The Panel is aware of the concept that it may be more convenient to include more than one active ingredient in the same product. Symptoms of the "common cold" or hay fever may include nasal congestion, running nose and coughing. The Panel has determined that if a combination product contains ingredients which are limited to one active ingredient from each representative pharmacologic group, e.g., nasal decongestant, antihistamine and antitussive, each of which is generally recognized as safe and effective when used alone for the specific symptom, e.g., antitussive for cough, the combination is rational and convenient for treatment of concurrent symptoms. The Panel concludes that the combinations of ingredients from pharmacologic groups identified below are safe and effective for a significant proportion of the target population having concurrent symptoms. (See part II. paragraph C.8.b. below—Criterion.)

The Panel clearly desires to avoid the so-called "shotgun approach" for the treatment of symptoms with a combination of ingredients in a single product. However, due to the unique nature of symptoms to be treated by CCABA preparations under consideration by this Panel, such combinations, with restrictions as established by the Panel, are justifiable.

The Panel is aware of a regulation (21 CFR 331.15(b)) providing for the combining of safe and effective (Category I) antacid and nonantacid active ingredients for the treatment of concurrent symptoms. The Panel emphasizes that the regulation provides for combining ingredients with different pharmacologic activities without additional clinical testing of the combination. This concept has been adopted by this Panel for certain combinations that the Panel has classified as Category I.

The Panel believes that these combinations of pharmacologic groups identified as Category I may offer a convenient and rational approach for relief of concurrent symptoms. The Panel has limited such combinations to three pharmacologic groups because it is unable to determine a significant target population which could benefit from a combination product containing greater than three pharmacologic groups. The Panel can find little scientific justification for including four or more pharmacologic groups in the same product since it is improbable that concurrent symptoms of sufficient duration and severity exist to warrant such combinations. As previously noted in the discussion pertaining to the "common cold," the course and symptoms of the disease are variable and may extend for 7 to 14 days. It would appear highly unlikely that at any one time, simultaneous symptoms would be present and of such severity in the course of the disease as to warrant the need for a product containing more than three pharmacologic groups. Therefore, the Panel has determined that combination products containing four or more different pharmacologic groups be classified as Category III. Before such products may be classified as Category I, a significant target population requiring such a combination for the treatment of concurrent symptoms of sufficient duration and severity must be identified.

4. *Combining of active ingredients reviewed by the Panel from the same pharmacologic group.* The Panel is concerned with the marketing of products containing drugs from the same pharmacologic group. Each Category I combination is currently limited to one active ingredient from any one pharmacologic group. The Panel can find little scientific justification for combining more than one active ingredient from the same pharmacologic group in the same product. The Panel is unaware of adequate supportive data which would establish sufficient argument for combining ingredients from the same pharmacologic group. For most products reviewed by the Panel, these ingredients from the same pharmacologic group are present in subtherapeutic doses. There is a lack of data on the effects of full therapeutic doses of ingredients from the same pharmacologic group in combination and therefore such combinations could not be evaluated by the Panel.

As an example, suppose two ingredients from the same pharmacologic group are combined in equal amounts in terms of pharmacologic activity (i.e., each at one-half the therapeutic dose) in the same product. The Panel doubts the justification in assuming that a dose of the product containing one-half the adult dose of each drug will produce an effect equal to one adult therapeutic dose of

either of the ingredients. The Panel is unable to find data to support the theory of the contribution of subtherapeutic doses of each ingredient in the same pharmacologic group in presently marketed combination products submitted for review to the Panel. The Panel is aware of certain combinations, such as "triple sulfas" to reduce the inherent toxicity of administering a single sulfa drug. However, this concept is difficult to relate to CCABA preparations since little evidence was submitted to the Panel demonstrating sufficient need for such combinations of ingredients from the same pharmacologic group.

It is the opinion of the Panel that to provide for combinations containing ingredients from the same pharmacologic group would contribute to the likelihood of undesirable additive or synergistic effects as noted above. (See part II. paragraph C.2. above—Limitation of ingredients in combination products.) It is accepted medical practice to give only those drugs necessary for the safe and effective treatment of the patient. The Panel believes that this concept should also apply to self-medication where a consumer treats symptoms without the advice of a physician.

In conclusion, to allow for the possibility, however unlikely, that there may be advantages to combining two drugs from the same pharmacologic group, the Panel has determined that such combination(s) be classified as Category III. Additional studies as described below in Principle No. 10 are needed for Category III combinations to determine their safety and effectiveness. (See part II. paragraph 10. below—Criteria and testing procedures for Category III combination products (for oral use unless otherwise specified).) The Panel has further determined that any combination product containing more than two active ingredients from the same pharmacologic group (e.g., three antihistamines) is irrational since there seems to be no reason to expect a possible benefit from the combination, and is therefore classified by this Panel as a Category II combination.

5. *Combining of active ingredients not reviewed by the Panel from the same or different pharmacologic group.* Many CCABA preparations contain active ingredients that have not been reviewed by this Panel because they are ingredients that have been or currently are being reviewed by other OTC panels. These ingredients include acetaminophen, aspirin, benzocaine, caffeine, quinine sulfate and salicylamide. Claims such as "temporarily relieves minor sore throat pain," or "For temporary relief of headache, aches, pains and fever due to colds" are examples of the labeling commonly found on CCABA preparations containing these ingredients. Such claims do not directly relate to the active ingredients reviewed by this Panel. The Panel has reviewed, for example, antitussives and the corresponding labeling claims for cough. However, the Panel has not reviewed analgesics and/or antipyretics for the labeling claims of pain and fever.

The Panel has evaluated the active ingredients in combination products submitted for review from the standpoint of their safe and effective use as cold, cough, allergy, bronchodilator and antiasthmatic products. Active ingredients included for concurrent symptoms, e.g., an analgesic for pain, have been reviewed only for their rational use in such combination products. The determination as to the safety and effectiveness of individual analgesics, for example, remains with the OTC Internal Analgesic Panel. The following are the Panel's conclusions as to the appropriateness of such combinations:

a. *Combination products containing vitamins.* The Panel is cognizant of the popular use of vitamin C (ascorbic acid) for the prevention or treatment of the "common cold." The Panel has reviewed the available data for the ingredient as a single entity and finds that the data are insufficient to permit final classification as safe and effective for OTC use in the prevention or treatment of the cold. The Panel has discussed the safety and effectiveness of vitamins including vitamin C as claimed active ingredients elsewhere in this document. (See part IX. paragraph B.1.b. below—Vitamins used alone or in combination CCABA products with labeling claims for the prevention or treatment of the "common cold.") and (See part IX. paragraph B.2.b. below—Ascorbic acid (vitamin C).) The Panel has also discussed the labeling of these claimed active ingredients elsewhere in this document. (See part IX. paragraph B.1.b. below—Vitamins used alone or in combination CCABA products with labeling claims for the prevention or treatment of the "common cold.") and (See part IX. paragraph B.2.b. below—Ascorbic acid (vitamin C).)

The Panel found no study which demonstrated that vitamin C is unequivocally effective for the prevention or treatment of the "common cold" although some data tended to favor effectiveness for treatment of cold symptoms. Since no conclusive data on the dose or dosage schedule are available on vitamin C used alone or in combination products with other ingredients for prevention or treatment of the cold, the Panel is unable to propose adequate labeling with a dosage regimen and has therefore classified such labeling as Category II. In summary, the Panel has reviewed vitamin C and has classified the "ingredient" as Category III and any "labeling" for the prevention or treatment of the cold as Category II.

With regard to combination products, the Panel further notes that the use of vitamins in CCABA combination products for the prevention of colds is irrational since the other ingredients in these products should only be used when the symptoms of the "common cold" are present. It is difficult for the Panel to rationalize the use of vitamin C or any other vitamin for the treatment of the "common cold" in combination products which are to be used only for a short duration while symptoms persist. It would be illogical for a consumer to take a cold combination product to prevent a cold. The Panel has therefore placed the labeling claims of combination products containing vitamins including vitamin C for prevention of the "common cold" in Category II.

b. *Combination products containing antihistamines with sleep-aid claims.* Antihistamines are primarily useful for relief of allergic disorders but secondarily act centrally to produce sedation or sleep. The Panel has discussed the safety and effectiveness of antihistamines elsewhere in this document. (See part VII. below—Antihistamines.) The Panel has established a safe and effective dosage range for certain antihistamines when used to treat symptoms of running nose, sneezing, itching nose or throat and watery eyes. The Panel has recommended that the labeling for these ingredients contain the warning, "May cause drowsiness".

The Panel notes that CCABA combination products are currently available for use at bedtime and promoted for such various claims as "for restful sleep". The Panel recognizes that if the symptoms of cough and cold are adequately treated, there is a greater likelihood of normal sleep. However, the duration of drug effects from "nighttime cold preparations" which are recommended to be taken once at bedtime is not fully documented.

The Panel is unable to make a final determination as to safe and effective use of an antihistamine or other agent when used as a sleep-aid in CCABA preparations. It is obvious an antihistamine may have several activities, e.g., antitussive, antihistamine, or sedative activity depending upon the dosage level used. The Panel has therefore placed sedation claims associated with CCABA combination products containing an antihistamine in Category III. The Panel further concludes that the combining of an additional antihistamine in a CCABA combination product for the exclusive purpose of sedation is irrational. Therefore, the Panel classifies such combinations as Category II.

c. *Combination products containing analgesics and antipyretics.* Many currently marketed combination products contain analgesics and antipyretics for treatment of concurrent symptoms of headaches, muscular aches, pains and fever which accompany colds. The Panel finds these claims to be acceptable and rational. Therefore, where not expressly prohibited, a generally recognized as safe and effective analgesic and/or antipyretic may be combined with the Category I ingredients reviewed by the Panel. Certain combinations that are contraindicated and placed in Category II are summarized below. (See part II. paragraph C.9. below—Criteria for Category II combination products (for oral use unless otherwise specified).)

d. *Combination products containing local anesthetics or other agents with*

claims for relief of sore throat. The symptoms of sore throat often accompany cough and the "common cold." It is usually a simple irritation aggravated by breathing through the mouth. The Panel has referred the evaluation of the safety and effectiveness of individual ingredients and labeling claims for sore throat to the OTC Oral Cavity Panel. The Panel believes that combination products containing safe and effective agents to relieve minor throat irritation are rational. The Panel has therefore placed combinations containing local anesthetics with other Category I CCABA agents in Category I. The Panel recommends that labeling contain adequate warnings against use when persistent or chronic sore throat is present and is accompanied by fever or other symptoms. (See part II. paragraph F. below—Deferral of "Sore Throat" Claim.)

The Panel recognizes that most sore throat remedies are applied topically while other symptoms of the cold are usually treated internally through oral ingestion. As an example, a throat lozenge containing a local anesthetic (benzocaine) and an antitussive (dextromethorphan) produces two pharmacologic activities. The lozenge releases benzocaine locally in the oral cavity whereas the dextromethorphan is ingested for a systemic action.

e. *Combination products containing correctives (stimulants and sedatives).* The Panel is aware that caffeine is included in some CCABA preparations with claims such as "for relief without drowsiness". Caffeine is also sometimes added to a combination product with no reference in the labeling as to its pharmacologic activity. The Panel presumes that the rationale for the inclusion of caffeine in such combinations is to reduce the sedating side effects of antihistamines.

While the Panel agrees with the rationale for caffeine serving as a "stimulant corrective," combinations containing it are placed in Category III until such "corrective" pharmacological action can be proven. This activity of caffeine should be identified on the label as "an ingredient added to counteract drowsiness caused by other drugs in this product." Where caffeine is added only as a corrective, labeling claims such as "for relief without drowsiness" are unjustified and are therefore misleading. The Panel has classified such labeling claims as Category II.

The Panel believes that combining Category I CCABA ingredients with a stimulant such as caffeine at a fully effective dose (not as a corrective) is irrational since the Panel is unaware of a significant target population having a need for CCABA ingredients and a stimulant. Accordingly, the Panel places combinations of CCABA ingredients combined with stimulants at effective dosage levels in Category II.

In addition, sympathomimetic drugs and theophyllines may cause central nervous system stimulation in some patients. To counteract this effect the Panel presumes that phenobarbital has been added to some combinations as a "sedative corrective" rather than as an active ingredient. While the Panel agrees with the rationale for phenobarbital serving as a "sedative corrective," combinations containing it are placed in Category III until such "corrective" pharmacologic action can be proven. (See part IX. paragraph B.2.d. below—Phenobarbital.) This activity of phenobarbital should be identified on the label as "an ingredient added to counteract nervousness caused by other drugs in this product." The Panel has included in this document a protocol designed to evaluate the effectiveness of phenobarbital under the above circumstances to show whether it has an additional beneficial or adverse effect on bronchospasm. (See part IX. paragraph B.2.d.(5) below—Evaluation.)

6. *Labeling of active ingredients.* As discussed above, the Panel has determined that each claimed active ingredient in a combination product must make a contribution to the claimed effect(s). (See part II. paragraph C.1. above—General combination policy.) Based upon this determination, the Panel concludes that combination products must be labeled to reflect all of the proven pharmacologic activities of each active ingredient in the combination. If a single ingredient has several activities, these should all be identified in the labeling consistent with the activities found at the recommended dosage for the product.

The Panel recommends that the labeling of a combination product containing active ingredients for treatment of concurrent symptoms emphasize the use of the product only when all such symptoms are present. The consumer should be adequately informed through the labeling of the therapeutic capabilities of the product. If, for example, only the symptom of running nose is present, a single ingredient rather than a combination product would be the rational therapy. Labeling should therefore fully reflect the activities of all active ingredients at the dosage recommended so that a consumer may select an appropriate product for relief of concurrent symptoms. If a product contains an active ingredient for which no labeling claim is made, it is clearly misleading to the consumer.

7. *Marketing experience for cold, cough, allergy, bronchodilator and antiasthmatic combination products.* The Panel recognizes the extensive marketing history of CCABA preparations. The drug industry presented data to the Panel summarizing consumer complaint information obtained from a survey of 32 pharmaceutical manufacturers (Ref. 2). A total of 117 combination CCABA products representing over 4 billion package units were included in the survey. The products were combinations of 83 ingredients representing 9 pharmacologic groups (nasal decongestants, antitussives, expectorants, antihistamines, anticholinergics, bronchodilators, analgesics, sedatives and stimulants). Inactive ingredients such as glycine and alcohol were also included in the data presented.

The drug industry reported to the Panel that the overall number of consumer complaints in the survey, in terms of either adverse reactions and/or ineffectiveness was less than one complaint per one million packages sold. However, from the survey data the Panel is unable to determine whether the information on adverse reactions was gathered during the entire period for which marketing data were reported for the products. The drug industry acknowledged that not every consumer complaint is well-founded or attributable to the drug product. In addition, not every consumer who fails to receive relief or experiences side effects registers complaints with the drug manufacturer.

The Panel has considered the marketing data submitted. The Panel finds that of the 83 ingredients included in the survey, only 11 ingredients have been classified by the Panel as Category I whereas 27 have been classified as Category III. Only one of the ingredients, belladonna alkaloids, has been classified as Category II when used by inhalation in the treatment of asthma. The remaining ingredients were not submitted for review to the Panel, pursuant to the call for data published in the FEDERAL REGISTER of August 9, 1972 (37 FR 16029), and therefore were not considered by the Panel. Several of these ingredients are currently available only by prescription while others are inactive ingredients. The actual quantities of active ingredients contained in the products and the amounts actually consumed by consumers were not included in the survey data and can only be estimated.

It would appear from the data that there is a low incidence of obvious adverse reactions which the consumer can attribute to the drug product. Since the quantities of drug administered in the surveyed products are not known, the Panel has reviewed the quantities of active ingredients contained in the marketed products submitted for review to the Panel. (See part I. paragraph A. above—Submissions by Firms.) The Panel presumes that the quantities of active ingredients contained in these products are generally representative of the products contained in the survey. The Panel concludes that while marketing data are limited and difficult to interpret they tend to support the safe use of combinations of active ingredients reviewed by the Panel.

The fact that over 4 billion packages of the 117 combination products have been sold would tend to indicate that consumers perceive a need for such drugs. It is obvious that consumers believe these products useful, to account for the many sales, but the extent to which this belief by the consumer is established by advertising rather than by a need perceived independently of advertising cannot be determined by the Panel. In addition, belief in the usefulness of a product may be related to a placebo response and also to the fact that a self-limiting illness is being treated.

Regarding effectiveness, the Panel has applied the OTC Drug Review Regulation (21 CFR 330.10(a)(4)(ii)) which provides, that as a source of corroboration for proof of effectiveness, the reports of significant human experience during

marketing are appropriate. The Panel finds the data helpful but not conclusive. The Panel believes that marketing experience, in and of itself, cannot be regarded as constituting adequate proof of effectiveness. Since the amounts of active ingredients included in the survey are not known, it is difficult for the Panel to determine the effectiveness of these combination products.

Data were contained in the survey of combinations by pharmacologic groups. For example, products with antitussives and nasal decongestants were compared to products containing antitussives, nasal decongestants and expectorants, etc. The data tend to indicate the addition of a drug from an additional pharmacologic group does not alter the complaint ratios. The Panel concludes that the data meet the criteria of the regulation (21 FR 330.10(a)(4)(ii)) and are limited but tend to support the effective use of certain combinations.

8. *Criteria for Category I combination products (for oral use unless otherwise specified).* Based upon an evaluation of the drug combinations submitted to the Panel for review, the following criteria have been established:

a. *Criterion.* Each claimed active ingredient and its labeling in a combination must be generally recognized as safe and effective (Category I) and each active ingredient must be combined within the established effective dosage range as set forth elsewhere in this document.

b. *Criterion.* Products containing one active ingredient from each pharmacologic group in the combinations identified below are classified as Category I combination products, provided the active ingredients and their labeling are generally recognized as safe and effective (Category I) and such ingredients are present in amounts within the effective dosage range.

(1) Combinations containing an analgesic-antipyretic and an antihistamine.

(2) Combinations containing an analgesic-antipyretic and a nasal decongestant.

(3) Combinations containing an analgesic-antipyretic, a nasal decongestant and an antihistamine.

(4) Combinations containing an antihistamine and an antitussive provided the product is labeled *"Caution:* May cause marked drowsiness." The labeling term "marked" relating to the warning statement may be removed if adequate data are supplied to the Food and Drug Administration to demonstrate that the combination product does not cause a significant increase in drowsiness as compared with each ingredient when tested alone.

(5) Combinations containing an antihistamine and a nasal decongestant.

(6) Combinations containing an antihistamine, an antitussive and a nasal decongestant.

(7) Combinations containing an antitussive and an expectorant provided the product is labeled only for nonproductive cough. Expectorants are expected to have their major usefulness in the irritative nonproductive cough as well as those coughs productive of scanty amounts of thick, sticky secretions. Antitussives suppress the act of coughing and may promote retention of some mucous secretions and thereby coat inflamed bronchial membrane linings.

(8) Combinations containing an antitussive and a nasal decongestant.

(9) Combinations containing an antitussive and a local anesthetic or local analgesic-antipyretic provided the product is available only as a lozenge.

(10) Combinations containing an antitussive, an expectorant and a nasal decongestant provided the antitussive and expectorant ingredients in the product are labeled only for nonproductive cough. Expectorants are expected to have their major usefulness in the irritative nonproductive cough as well as those coughs productive of scanty amounts of thick, sticky secretions. Antitussives suppress the act of coughing and may promote retention of some mucous secretions and thereby coat inflamed bronchial membrane linings.

(11) Combinations containing an oral bronchodilator and an expectorant provided the product is labeled only for cough associated with asthma.

(12) Combinations containing an oral bronchodilator (sympathomimetic) and an oral bronchodilator (theophylline).

(13) Combinations containing an expectorant and a nasal decongestant.

(14) Combinations containing a nasal decongestant and a local anesthetic or local analgesic-antipyretic provided the product is available only as a lozenge.

9. *Criteria for Category II combination products (for oral use unless otherwise specified).* Based upon an evaluation of the drug combinations submitted to the Panel for review, the following criteria have been established:

a. *Criterion.* A combination is Category II if a Category II ingredient or labeling is present in the combination product.

b. *Criterion.* A combination product containing Category I ingredients from different pharmacologic groups is classified as Category II if it includes any ingredient(s) at less than the minimum effective dosage established by the Panel unless the ingredient(s) are being used to treat the same symptom. (See Part II. paragraph C. 10.b.(1) below—Category III Combination.)

c. *Criterion.* If a product contains an active ingredient or labeling that has not been reviewed by this or other OTC Advisory Review Panels, such ingredient or labeling is classified by this Panel as Category II.

d. *Criterion.* A combination product is classified as Category II if it includes more than two active ingredients from the same pharmacologic group.

e. *Criterion.* Combinations of active ingredients and labeling which have been determined by the Panel to be unsafe or irrational and classified as Category II are as follows:

(1) Combinations containing an analgesic-antipyretic and a bronchodilator. This combination contains an analgesic for the symptomatic treatment of fever or muscular aches, etc., associated with the "common cold" and contains a bronchodilator with a claim for the treatment of symptoms of asthma. The Panel concludes that if an individual with a cold needs relief of asthma, he should take a bronchodilator separately since there may be a more frequent need of this drug than for the other ingredients contained in the preparation. In addition, the Panel further concludes that a bronchodilator should only be labeled for use in patients with asthma and that the addition of an analgesic is irrational. The Panel believes that for treatment of concurrent symptoms where an asthmatic requires an analgesic or antipyretic, he should take such drugs separately because the dosage and need for each of the ingredients varies with the likelihood that the bronchodilator is more frequently required.

(2) Combinations containing an anticholinergic and an expectorant. This combination is irrational because an expectorant promotes the production of secretions whereas the anticholinergic produces an opposite effect, i.e., anti-secretory action.

(3) Combinations containing an antihistamine and an expectorant. This combination is irrational because an expectorant promotes the production of secretions whereas the anticholinergic activity of an antihistamine produces an opposite effect, i.e., anti-secretory action.

(4) Combinations containing a bronchodilator and an anticholinergic. This combination is irrational because the anti-secretory action of the anticholinergic may produce thickened bronchial secretions which may cause further obstruction of the airways in individuals with asthma.

(5) Combinations containing a bronchodilator and an antihistamine. This combination is irrational because the anticholinergic effect, i.e., anti-secretory action, of antihistamines may produce thickened bronchial secretions which may cause further obstruction of the airways in individuals with asthma.

(6) Combinations containing an oral bronchodilator and an antitussive when the product is labeled only for cough associated with asthma. This combination is irrational because the antitussive suppresses cough and the cough reflex is essential in asthma to maintain an open airway by clearing the respiratory passages of excessive secretions.

(7) Combinations containing an antitussive and an antihistamine if the antitussive is also generally recognized as safe and effective as an antihistamine. This combination is not safe because the antihistaminic side effects of the antitussive may combine with the side effects of the antihistamine.

(8) Combinations containing an antihistamine and an antitussive if the antihistamine is also generally recognized as safe and effective as an antitussive. This combination is not safe because the antitussive side effects of the antihistamine may combine with the side effects of the antitussive.

f. *Criterion.* Combination products containing any vitamins, e.g., vitamin C, with labeling claims which represent or

suggest the product for the prevention or treatment of the "common cold". (See part II. paragraph C.5.a. above—Combination products containing vitamins.)

g. *Criterion.* Combination products containing a stimulant, e.g., caffeine, at a fully effective level (not as a "corrective"). (See part II. paragraph C.5.e. above—Combination products containing correctives (stimulants and sedatives).)

h. *Criterion.* Combination products containing more than one antihistamine in which an additional antihistamine is added for the exclusive purpose of sedation and the product contains labeling which represents or suggests the additional antihistamine as a "sleep-aid." (See part II. paragraph C.5.b. above—Combination products containing antihistamines with sleep-aid claims.)

10. *Criteria and testing procedures for Category III combination products (for oral use unless otherwise specified).* Based upon an evaluation of the drug combinations submitted to the Panel for review the following criteria and corresponding testing procedures are recommended:

a. *Criterion.* (1) *Category III combination.* If a Category III ingredient or labeling is present in a combination product containing no Category II ingredient or labeling, the combination is classified as Category III.

(2) *Category III testing procedure.* The Category III ingredient (or ingredients) for the labeling claims (symptom(s)) must be tested in accordance with the evaluation protocol specified for that particular pharmacologic group. The appropriate protocol(s) under the heading "Data Required for Evaluation" are identified elsewhere in this document for each respective pharmacologic group. If when tested alone the Category III ingredient (or ingredients) can be shown to be safe and effective in accordance with the standards for evaluation established in the protocol(s), it then qualifies for Category I status. The combination will then contain only Category I ingredients and will be considered Category I without further testing provided the combination is identified above. (See part II. paragraph C.8.b. above—Criterion.)

b. *Criterion.* (1) *Category III combination.* If two or more ingredient(s) are being used to treat the same symptom (labeling claim), a combination product is classified as Category III even if it contains Category I ingredients from different pharmacologic groups when any ingredient(s) is present at less than the minimum effective dosage established by the Panel.

(2) *Category III testing procedure.* An acceptable test procedure will be one in which the combination, each of the individual ingredients in the minimum effective dosage, and each of the individual ingredients in the less than the minimum effective dosage used in the combination, and a placebo are evaluated, all in the same study, against the relevant symptom (labeling claim). In this way, comparisons of safety and effectiveness can be made directly between the combination, the individual ingredients and the placebo. The appropriate protocol(s) under the heading "Data Required for Evaluation" are identified elsewhere in this document for each respective pharmacologic group. Each individual ingredient which is in less than the minimum effective dosage should demonstrate a contribution, but not necessarily a significant effect, against the relevant symptom when compared to placebo. It is very difficult to develop a generally applicable definition of a "contribution." Each ingredient and the symptom that it should affect must be analyzed individually as to the effect on the patient population in which it is being used. For an ingredient to be judged as contributing to the alleviation of the relevant symptom, the Panel suggests that the drug effect should demonstrate a 10 percent or greater difference from placebo.

For a combination of Category I ingredients from different pharmacologic groups used to treat the same symptom and in which at least one of the ingredients is in less than the minimum effective dosage, to be classified as a Category I combination, the relative incidence of side effects and/or other untoward effects of the combination should not be significantly greater than those of any individual ingredient in that combination alone in the minimum effective dosage. In addition, the combination must exert a significant effect against the relevant symptom which is not less than any one of the ingredients when tested alone in the minimum effective dosage. The justification for these requirements is that such a combination should not compromise effectiveness nor should it pose a greater risk of side effects than is associated with an ingredient alone in its minimum effective dosage.

c. *Criterion.* (1) *Category III combination.* A combination product is classified as Category III if it includes two Category I ingredients from the same pharmacologic group.

(2) *Category III testing procedure.* An acceptable test procedure will be one in which the combination, each of the individual ingredients, at its minimum effective dosage, and a placebo are evaluated, all in the same study, against the relevant symptom (labeling claim). In this way, comparisons of safety and effectiveness can be made directly between the combination, the individual active ingredients from the same pharmacologic group at its minimum effective dosage and the placebo. The appropriate protocol(s) under the heading "Data Required for Evaluation" are identified elsewhere in this document for each respective pharmacologic group.

For a combination of two Category I ingredients from the same pharmacologic group to be classified as a Category I combination, the relative incidence of side effects and/or other untoward effects of the combination should not be significantly greater than those of either individual ingredient alone at its minimum effective dosage. In addition, the combination must exert a significant effect against the relevant symptom(s) which is not less than either one of the ingredients when tested alone at its minimum effective dosage. The justification for these requirements is that such a combination should not compromise effectiveness nor should it pose greater risk of side effects than is associated with an individual ingredient alone.

d. *Criterion.* (1) *Category III combination.* A combination product containing two Category I ingredients from the same pharmacologic group is classified as Category III if it includes either or both ingredient(s) at less than the minimum effective dosage established by the Panel.

(2) *Category III testing procedure.* An acceptable test procedure will be one in which the combination, each of the individual ingredients in the minimum effective dosage, and each of the individual ingredients in the less than the minimum effective dosage used in the combination, and a placebo are evaluated, all in the same study, against the relevant symptom. In this way, comparisons of safety and effectiveness can be made directly between the combination, the individual active ingredients from the same pharmacologic group and the placebo. The appropriate protocol(s) under the heading "Data Required for Evaluation" is identified elsewhere in this document for each respective pharmacologic group. Each individual ingredient which is in less than the minimum effective dosage should demonstrate a contribution, but not necessarily a significant effect, against the relevant symptom when compared to placebo. It is very difficult to develop a generally applicable definition of a "contribution." Each ingredient and the symptom that it should affect must be analyzed individually as to the effect on the patient population in which it is being used. For an ingredient to be judged as contributing to the alleviation of the relevant symptom, the Panel suggests that the drug effect should demonstrate a 10 percent or greater difference from placebo.

For a combination of two Category I ingredients from the same pharmacologic group to be classified as a Category I combination, the relative incidence of side effects and/or other untoward effects of the combination should not be significantly greater than those of either individual ingredient alone in the minimum effective dosage. In addition, the combination must exert a significant effect against the relevant symptom which is not less than either one of the ingredients when tested alone in the minimum effective dosage. The justification for these requirements is that such a combination should not compromise effectiveness nor should it pose greater risk of side effects than is associated with an individual ingredient alone in the minimum effective dosage.

e. *Criterion.* (1) *Category III combination.* Combinations of active ingredients for which the available safety data are insufficient for the Panel to make a final

determination and are classified as Category III: (i) Combinations containing atropine and an oral nasal decongestant. Additional studies are necessary to assess the potential additive central nervous system stimulant side effects.

(ii) Combinations containing an antihistamine and an anticholinergic. Additional studies are necessary to assess the nature and extent of additive anticholinergic side effects.

(2) *Category III testing procedure.* An acceptable test procedure will be one in which the combination and a placebo are evaluated in suitable subjects so that comparisons can be made of the particular side effect(s) of concern which are specified above. In addition, data on the relative incidence and intensity of those side effects must be available for the individual active ingredients in the same dosage as in the combination either evaluated in the same study as above, or evaluated in a separate study using a comparable test protocol. The appropriate protocol(s) under the heading "Data Required for Evaluation" are identified elsewhere in this document for each respective pharmacologic group.

If the relative incidence and intensity of the side effect(s) of the combination are increased to a degree which prevents its safe use as an OTC product, it will be classified as a Category II combination for those dosages. If the relative incidence and intensity of side effect(s) are significantly greater than with either ingredient administered alone but not to a degree to prevent its safe OTC use, a suitable warning regarding potential for that side effect should be specified in the labeling for the combination product. If the relative incidence and/or intensity of side effect(s) with the combination are not significantly greater than with either ingredient administered alone, no warnings other than the standard Category I warnings for those ingredients are needed on the label.

f. *Criterion.* (1) *Category III combination.* Combinations of active ingredients for which the available effectiveness data are insufficient for the Panel to make a final determination or for which there is no rationale for use and are classified as Category III are as follows: (i) Combinations containing a nasal decongestant and an antihistimine administered topically as a spray or drops. Additional studies are necessary to assess the contribution of the antihistamine administered by the topical route since there are inadequate studies demonstrating the effectiveness of the antihistamines topically in such combinations.

(ii) Combination products containing an antitussive and a bronchodilator used as an antitussive provided the product is labeled only for cough not associated with asthma. Additional studies are necessary to assess the antitussive effects of a bronchodilator in combination with an antitussive in reducing cough.

(iii) Combination products containing an expectorant and a bronchodilator used as an antitussive provided the product is labeled only for cough not associated with asthma. Additional studies are necessary to assess the antitussive effects of a bronchodilator in combination with an expectorant in reducing cough.

(iv) Combination products containing an antitussive and an expectorant provided the product is labeled only for productive cough. Additional studies are necessary to assess the combined effects of an antitussive and an expectorant in the presence of excessive or more fluid bronchial secretions.

(v) Combination products containing an antitussive, an expectorant and a nasal decongestant provided the antitussive and expectorant ingredients in the product are labeled only for productive cough. Additional studies are necessary to assess the combined effects of an antitussive and an expectorant in the presence of excessive or more fluid bronchial secretions.

(2) *Category III testing procedure.* An acceptable test procedure will be one in which the combination, each individual ingredient, and a placebo are evaluated against the relevant symptoms either in the same study or in separate studies using comparable test protocols. The appropriate protocol(s) under the heading "Data Required for Evaluation" is identified elsewhere in this document for each respective pharmacologic group. In this way, comparisons of effectiveness can be made between the combination, the individual active ingredients and the placebo by that route of administration. When tested alone by that route of administration, each individual ingredient should demonstrate a significant effect against the relevant symptom when compared to placebo.

For the combination of Category I ingredients from different pharmacologic groups to be a Category I combination by that route of administration, the combination must also exert a significant effect against each of the relevant symptoms when compared with the placebo.

g. *Criterion.* (1) *Category III combination.* Combination products containing an active ingredient specifically intended to counteract a side effect of other ingredients in the product, i.e., a "corrective", for which the available data are insufficient for the Panel to make a final determination, are classified as Category III.

(2) *Category III testing procedure.* An acceptable test procedure will be one in which the combination with and without the corrective is evaluated to assess the effectiveness of the corrective to significantly decrease the incidence and/or intensity of the undesirable side effect, and to assess the safety of this combination.

h. *Criterion.* (1) *Category III combination.* Combination products containing an antihistamine with a sleep-aid claim for which data are insufficient for the Panel to make a final determination and are classified as Category III.

(2) *Category III testing procedure.* If a sleep-aid effect is claimed for the antihistamine, the Panel recommends a testing protocol in conformance with requirements specified by the OTC sedative, tranquilizer and sleep-aid drug products Panel as published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292).

i. *Criterion.* (1) *Category III combination.* Combination products containing several claimed active ingredients which are mixtures of volatile substances with overlapping pharmacologic activities for which a minimum effective dosage cannot be established for one or more of the ingredients when tested alone are classified as Category III.

(2) *Category III testing procedure.* An acceptable test procedure will be one in which the combination, each of the individual ingredients in the dosage used in the combination, and a placebo must be evaluated against the relevant symptom (labeling claim), either in the same study, or in separate studies using comparable test protocols. The appropriate protocol(s) under the heading "Data Required for Evaluation" are identified elsewhere in this document for each respective pharmacologic group. When tested alone, each individual ingredient should demonstrate a contribution, but not necessarily a significant effect, against the relevant symptom when compared to placebo. It is very difficult to develop a generally applicable definition of a "contribution." Each ingredient and the symptom that it should affect must be analyzed individually as to the effect on the patient population in which it is being used. For an ingredient to be judged as contributing to the alleviation of the relevant symptom, the Panel suggests that the drug effect should demonstrate a 10 percent or greater difference from placebo.

For the combination of these ingredients to be classified as Category I, it must exert a significant effect against the relevant symptom when compared to placebo meeting the standards of evaluation set forth for that pharmacologic group. Furthermore, the combination product must be judged safe for OTC use as evaluated by the incidence and/or intensity of side effects and/or other untoward effects.

j. *Criterion.* (1) *Category III combination.* There is lack of data on a suitable target population with concurrent symptoms of sufficient duration to justify combination products containing four or more different pharmacologic groups. Therefore, the Panel classifies combination products containing four or more different pharmacologic groups as Category III. Examples of such combinations are as follows:

(i) Combinations containing an analgesic-antipyretic, an antitussive, an expectorant and a nasal decongestant.

(ii) Combinations containing an analgesic-antipyretic, an antitussive, an antihistamine and a nasal decongestant.

(2) *Category III testing procedure.* Before such combinations may be classified as Category I, a significant target population requiring such a combination for the treatment of concurrent symptoms of sufficient duration and severity must be identified by appropriate epidemiological studies. If a suitable target population is

found such combinations may be classified as Category I.

REFERENCES

(1) "AMA Drug Evaluations," 2d Ed., American Medical Association, Chicago, pp. 499–503, 1973.

(2) OTC Volume 040287.[1]

(3) Cohen, B. M., "Sympathomimetic/Xanthine Broncholysis in Obstructive Ventilatory Disorders," *International Journal of Clinical Pharmacology*, 9:6–15, 1974.

D. STATEMENT ON CATEGORY III TESTING PROCEDURES

1. *Comments on study design.* The Panel has agreed that the protocols recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved technology in the future.

Experimental design should take into account the need to include a sufficient number of subjects or trials so as to provide meaningful conclusions which can be supported by appropriate statistical analysis. The selection of appropriate subjects or patients can be of major importance when the effect of a drug in a specific illness or symptom is under study.

A role for bias is assumed in all situations wherein the subject, the observer or both make a judgment as to the nature of magnitude of a response. Biological factors also contribute to variation in response between individuals in a given study sample. Although bias and biological variation cannot be eliminated, their effect on the outcome of an experiment can be avoided or minimized by adopting a "double-blind, placebo-controlled" or other suitably blinded design. In such a design, one group of subjects receives a placebo or dummy preparation so that the response unmodified by drug under test can be established. Neither the subjects nor the observer should be able to detect the identity of the preparations under test. This requires that the test and placebo preparations be indistinguishable in regard to taste, color and shape except in the case of preparations containing volatile substances where it will be impossible to make the active ingredients indistinguishable from the placebo.

It is often desirable to include a standard drug (a drug used as a positive control known to exert a significant effect against the relevant symptom(s) being tested) with which the unknown can be compared. Finally the inclusion of two or more dose levels of the drug under test may be desirable in order to provide an estimate of an effective therapeutic dose range free from undesirable side effects. If a crossover design is utilized, i.e., each subject serves as his own control, the sequence in which the placebo, standard and test drugs are administered should be randomized and a sufficient "washout period" between tests should be permitted.

Wherever possible, objective measurements should be made in perference to subjective judgments. However, such measurements should be relevant to the symptom or symptom complex for which the drug under test is to be used.

2. *Testing period provided for Category III conditions.* The Panel concludes that the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient (Category III) to classify such conditions either as Category I—generally recognized as safe and effective and not misbranded, or as Category II—not being generally recognized as safe and effective, or would result in misbranding be permitted to remain in use for the period of time specified below after the date of publication of the final monograph in the FEDERAL REGISTER, if the manufacturer or distributor of any such drug utilizing such conditions in the interim conducts tests and studies adequate and appropriate to satisfy the questions raised with respect to the particular condition by the Panel.

The Panel has established the following specific time limitations for testing based upon the applicable pharmacologic group:

	Time provided for testing (years)
Pharmacologic group:	
Anticholinergic	3
Antihistamine	3
Antitussive	4
Bronchodilator sympathomimetic	3
Bronchodilator theophylline	3
Expectorant	5
Nasal decongestant	3

The Panel believes that testing for bronchodilators, antihistamines, anticholinergics and nasal decongestants can be completed within 3 years. The techniques for testing are all well-established and are discussed in the relevant sections of the document below. The Panel feels that 1 year is necessary for the development of protocols with 2 years provided for the actual testing. Clinical testing should start within 6 months of publication of the final monograph.

The techniques for testing antitussives involve cough counting. At present, there are relatively few laboratories available to do this work, and the techniques are very time-consuming. Because of these factors, 4 years have been provided as the time limitation. Clinical testing should start within 1 year of the publication of the final monograph.

The Panel recognizes that the evaluation of expectorants is difficult and there is no completely accepted technique available for the assessment of this pharmacologic group of drugs. It seems likely that new techniques will have to be developed for effective testing of these substances. Because of the need for developmental technical work, the time limitation is placed at 5 years. Clinical testing should start within 18 months of the publication of the final monograph.

The Panel concludes that for Category III combination drug products containing more than one pharmacologic group, the time established for testing shall be determined by the pharmacologic group having the longest period provided for testing. (See part II. paragraph C.10 above—Criteria and testing procedures for Category III combination products (for oral use unless otherwise specified).)

In addition to establishing time limitations of testing for specific pharmacologic groups, the Panel has established the following periods for testing of other Category III conditions:

	Time provided for testing (years)
Category III condition:	
Antihistamines with sleep-aid claims	3
Caffeine (stimulant corrective)	2
Phenobarbital (sedative corrective)	2
Timed-release drug formulations	4
Vitamin C (ascorbic acid)	3

The Panel recognizes that CCABA combination products are available for use at bedtime and promoted for such various claims as "for restful sleep." The Panel has discussed sleep-aid claims elsewhere in this document (See part II. paragraph C.5.b. above—Combination products containing antihistamines with sleep-aid claims).

The Panel is unable to make a final determination as to safe and effective use of antihistamines or other agents as sleep-aids in CCABA preparations. The Panel has therefore placed sedation claims associated with CCABA combination products containing antihistamines in Category III and has provided 3 years for testing and documentation of such claims.

The Panel is aware that caffeine is included in some CCABA preparations with claims such as "for relief without drowsiness". Caffeine is also contained in combination products with no reference in the labeling as to its pharmacologic activity. The Panel presumes that the rationale for the inclusion of caffeine in such combinations is to reduce the sedating side effects of antihistamines. The Panel has discussed the use of "stimulant correctives" elsewhere in this document. (See part II. paragraph C.5.e. above—Combination products containing correctives (stimulants and sedatives).) The Panel agrees with the rationale for caffeine serving as a "stimulant corrective" but combinations containing it are placed in Category III until such "corrective" pharmacological action can be proven. The Panel has provided 2 years for testing and documentation of such claims.

Timed-release drug formulations have been reviewed elsewhere in this document. (See part II. paragraph E. below—Effect of Timed-Release Formulations on Effectiveness and Safety of OTC Drug

[1] Cited OTC Volumes refer to the submissions made by interested persons pursuant to the call for data notice published in the FEDERAL REGISTER of August 9, 1972 (37 FR 16029). The volumes are on file in the office of the Hearing Clerk, Food and Drug Administration, Room 4–65, 5600 Fishers Lane, Rockville, MD 20852.

Products.) The Panel has provided 4 years for the development of suitable tests for the standardization of all OTC timed-release CCABA products.

Vitamin C (ascorbic acid) has been reviewed elsewhere in this document. (See part IX. paragraph B.1.b. below—Vitamins used alone or in combination CCABA products with labeling claims for the prevention or treatment of the "common cold" and part IX. paragraph B.2.b. below—Ascorbic acid (vitamin C).)

The Panel concludes that the effectiveness of vitamin C in the prevention or treatment of the "cold" has not been established and has classified the ingredient as Category III with 3 years provided for testing. However, all labeling claims for the ingredient for the prevention or treatment of the "cold" are classified as Category II.

Phenobarbital has been reviewed elsewhere in this document. (See part II. paragraph C.5.e. above — Combination products containing correctives (stimulants and sedatives) and part IX. paragraph B.2.d. below—Phenobarbital.) Several products used in the treatment of the symptoms of asthma contain drugs which stimulate the central nervous system in some patients. The Panel presumes that phenobarbital is included to counteract these effects and is therefore a "sedative corrective" rather than an active ingredient. The Panel agrees with the rationale for phenobarbital serving as a "sedative corrective" but has classified such combinations as Category III until such "corrective" action is proven. The Panel has provided 2 years for testing and documentation of such claims.

E. EFFECT OF TIMED-RELEASE FORMULATIONS ON EFFECTIVENESS AND SAFETY OF OTC DRUG PRODUCTS

1. *Introduction.* The oral route is the most common method of administration for OTC cold, cough, allergy, bronchodilator and antiasthmatic products. Such products are swallowed and absorbed from the stomach and intestines. Drugs administered orally are dissolved in gastrointestinal fluids and are absorbed into the systemic circulation where they exert an action on "target" organs or receptors. Generally, this action occurs within an hour or so of ingestion of the drug and peaks, e.g., in an hour or two, but the drug action lasts for several hours, e.g., 3 to 6 hours. When the drug action begins to decline, e.g., at the end of 3 to 6 hours, it is necessary to take another dose so that the desired action will continue at a more or less constant level. Most drug studies showing safety and effectiveness have been carried out with oral dosage forms that act in this manner. There are, however, a number of OTC CCABA products that are formulated in another kind of oral dosage form called timed-release formulations. Theoretically, these products are formulated so as to dissolve in gastrointestinal fluids in a controlled manner so that small amounts will be absorbed over a longer period of time, e.g., over 3 to 6 hours rather than 1 hour, and the duration of drug action will be extended over a longer period, e.g., 8 to 12 hours rather than 3 to 6 hours.

Since the specific formulation of a product can affect its safety and effectiveness, the Panel has considered timed-release formulations of OTC products under its review. The Panel did not consider in detail each of these formulations nor evaluate the dissolution times of the specific formulation or the affect of formulation on safety and effectiveness of each individual ingredient under review when formulated in this unique manner. The Panel does recognize certain advantages and disadvantages of timed-released formulations. The Panel has reviewed the pertinent literature and selected articles regarding timed-release formulations and has set forth certain guidelines to be used in their evaluation (Refs. 1 through 9).

2. *General discussion.* To produce its characteristic effect, a drug must achieve adequate concentrations at its site of action. One important factor in determining the concentration attained is the extent and rate of drug absorption. Other factors include the amount of drug administered, its distribution within the body, binding or localization in tissues, inactivation or metabolism and excretion.

The latent period between administration of a drug and its onset of action is influenced by the route of administration, e.g., orally, topically, by inhalation, etc., and the rate of absorption and the penetration of the drug at the site of action. The duration of drug effects is determined largely by the rate of inactivation and excretion of the drug. The duration of action of the drug effect is determined by a balance between all of these factors.

The rate of absorption of oral dosage forms is dependent mainly on their dissolution rate in gastrointestinal fluids. Theoretically, slow release and sustained effects (up to 8 hours or longer) of drugs administered in oral dosage forms should be attained if such drugs are formulated so as to dissolve in gastrointestinal fluids in a controlled manner.

A number of the active ingredients reviewed by the Panel are presently formulated in repeat action or extended release dosage forms. These formulations are known by a variety of names such as sustained action, sustained release, prolonged release, controlled release, long-acting time release, etc. Repeat-action tablets periodically release complete doses of active drug to the gastrointestinal fluids. Extended-release tablets continuously release increments of the contained medication to the gastrointestinal fluids. These terms are often used interchangeably and, although technically different, are referred to in this document as timed-release formulations.

3. *Advantages.* The principle of controlled release of drugs from oral dosage units is generally accepted to provide several advantages over the conventional dosage forms that require a shorter time interval regimen of administration.

Among these advantages may be listed the principal ones of better patient compliance, increased patient convenience, and lower incidence and/or severity of side effects of the drugs due to elimination of the peaks in the level of drug concentration in the blood that often occur after repeated administration of traditional dosage forms.

4. *Disadvantages.* Among the disadvantages is the fact that uniformly effective preparations of time-released drugs have been difficult to achieve, in part because of technical problems associated with their manufacture, but also because the dissolution rate of these preparations in gastrointestinal fluids may be irregular and because variations in gastrointestinal acidity, gastric emptying, and intestinal motility and other physiological factors also influence drug absorption.

If reasonable uniformity of effectiveness is not achieved, for whatever reason, the dissolution rate, for example, may be so slow that no effect is achieved or, conversely, it may be so fast that the patient receives the effect of all the active drug within a short time period, resulting in an increased incidence and/or severity of side effects.

On theoretical grounds, there are a number of reasons why a given drug should not be formulated as a timed-release product. These reasons relate to the inherent nature of a specific drug. For example, a drug may have a very long half-life, i.e., it may be metabolized and eliminated from the body over a long period of time, and thus conventional dosing already provides sustained blood levels. A drug may require a very large dose before sustained action is possible and a timed-release product containing a dose sufficient for 8 or 12 hours would necessitate an inconvenient amount of drug being swallowed. Potent drugs, i.e., those having a very small difference between the effective and toxic doses, or those to which patient response is variable, necessitate individualization of dose or dosage interval, and timed-release products are designed to release the drug in a fixed pattern. Drugs that are poorly absorbed or poorly soluble are likely to be absorbed erratically, and thus the predictability of response following ingestion of a timed-released product is difficult. Since the amount of drug contained in a timed-release formulation is usually greater than in a conventional formulation, increased side effects or toxicity is possible. Variations in the patient's physiological response or a technical flaw in the formulation may result in the release of the entire amount of active drug from the formulation in a short period of time, thus producing adverse reactions.

Some drugs reviewed by the Panel are inappropriate for formulation in a timed-release product. Glyceryl guaiacolate is a drug that for effectiveness requires a relatively large dose at regular intervals. Thus, the dose of the drug required to obtain an effective action over an extended period of time, e.g., 8 to 12 hours, would be difficult to swallow. The theophyllines represent an example of a potent drug for which patient dosage should be individualized because of the drugs' variable rates of metabolism. Such

individualization of dosage is best obtained by ingestion of small doses of theophyllines at more frequent intervals than are possible with timed-release products.

All other drugs reviewed by the Panel would, on theoretical grounds, be suitable for incorporation into a timed-release product. For approval of any drug in a given type of timed-release formulation, evidence should be presented to demonstrate that blood levels or clinical effects are comparable and the incidence of side effects is not greater than that seen when compared to the preparation given in repeated, single doses (conventional dosage).

5. *Guidelines for evaluation of timed-release formulations.* Timed-release formulations generally fall into one of three major categories: Extended release—those that provide for gradual and continuous release of active substance along the gastrointestinal tract; repeated action—those that provide two or more essentially discrete release times for the active constituents, e.g., coat/core formulations; and those that combine the mechanisms of both of the foregoing kinds of formulations.

Evaluation of any type of long-acting oral formulation should accomplish two objectives. First, it should establish that the dosage form provides delayed absorption of all or part of the drug(s) as claimed in the labeling. Secondly, it should establish that the formulation delivers the claimed dosage of the drug(s) to the patient.

There are basically two major methods of evaluating these specialized dosage forms:

a. *Clinical methods.* Controlled clinical tests, aimed at measuring the magnitude and duration of either the therapeutic effect or a characteristic pharmacologic effect resulting from timed-release drug as compared to the concentration or drug activity resulting from the usual dose administered in solution or a rapidly disintegrating solid dosage form, offers an ideal way of determining the safety and effectiveness of a timed-release dosage form of a drug. Unfortunately, however, there are few objective measurements currently available that will demonstrate drug action even though there are pharmacologic responses (see other sections of this document describing evaluation protocols for clincial studies). Where such methods are available, they should be the evaluative method of choice to compare the timed-release product with suitably repeated doses of the drug in a conventional formulation. In the absence of clinical trials of timed-release preparations, blood levels and urinary excretion determinations are acceptable if these measurements can be related to pharmacologic effects.

b. *Drug absorption methods.* (1) *Blood level measurements.* Long-acting dosage forms can be evaluated by methods that measure the rate and extent to which the active ingredients are absorbed into the bloodstream. A principal way of determining this drug absorption makes use of tests in which the blood levels of the drug are measured at specified time intervals after administration of the product.

The analytical method should permit quantitative evaluation of rates of absorption, peak drug levels, and peak time and areas under blood drug-level curves. The latter are particularly useful in evaluation of time-release formulations because the area under the blood drug-level curve of such a formulation should approximate that obtained with appropriately repeated doses of a conventional oral form of the drug. Thus, for example, two experimental approaches may be considered: For coat/core formulations, the aim is to establish whether the release time of each ingredient corresponds to the labeling claim, and then to determine whether the blood-level curve obtained with the core approximates that obtained with conventional tablets; and for other timed-release formulations one can also compare blood levels with those of a conventional form of the drug when each preparation has been administered at recommended time-intervals.

Where appropriate, it is preferable to measure blood levels of the parent drug and/or its metabolites; however, urinary excretion measurements offer an alternative approach.

(2) *Urinary excretion measurements.* There are many instances where adequate reproducible methods of determining blood levels have not yet been developed. In which case, urinary analytical methods offer an alternative to blood level measurements in evaluating a timed-release oral form of a drug. Urinary excretion measurements can provide quantitative data only when the drug is excreted unchanged in the urine or when the metabolism of the drug is well understood. In utilizing measurements of urinary levels and excretion rates, the timed-release product should also be compared with suitably repeated doses of a conventional oral form of the drug. With both preparations, the urinary excretion levels and rates over the test period should be roughly similar but need not be equal.

6. *Summary.* If claims of timed-release are made, these claims must be supported by evidence as compared to usual suitably repeated doses of the drug in a conventional oral formulation. Such evidence should be obtained from studies in humans, which are based upon the measurement of a therapeutic effect or acute pharmacologic effect of the drug or may be based upon the blood level and/or excretion characteristics of the drug.

The results obtained by suitable clinical methods or by blood level or urinary excretion methods should be correlated with appropriate in vitro dosage performance tests defined by the manufacturer. The in vitro tests should be incorporated into the quality control procedures as part of the Food and Drug Administration's regulations on good manufacturing practices identified in 21 CFR Part 211. The ongoing in vitro quality control procedure would assure product performance on a level in consonance with the in vivo results obtained during the initial stages of development of the particular timed-release product.

The Panel has reviewed § 200.31 (21 CFR 200.31) of the regulations, which regards a timed-release dosage form as a new drug when any such dosage form contains per dosage unit a quantity of active ingredient that is not generally recognized as safe (GRAS) for administration as a single dose under the conditions suggested in the labeling. In such cases, a new drug application (NDA) is required to demonstrate that the drug is properly formulated to release at a safe rate the total dose contained per dosage unit.

The Panel is concerned with the issue of sustained-release formulations of active ingredients placed in Category I. This concern relates to approval of dosage levels of Category I active ingredients in excess of the maximum effective dosage per dosage unit based upon sustained-release or timed-release characteristics of the particular product.

The issue facing the Panel is whether to recommend to the agency that timed-release products be reviewed on a product-by-product basis through the new drug application procedures or whether suitable standards can be developed for testing which can be included in the CCABA drug monograph. The Panel views the exclusive use of the new drug application procedures as eliminating any possible general recognition for timed-release products. The Panel is aware that the drug industry has developed appropriate test procedures for specific timed-release mechanisms which would assure that various timed-release products deliver an effective dosage of active ingredient over a claimed extended period of time between, e.g., 8 and 12 hours. The Panel encourages the drug industry with the assistance of the Food and Drug Administration to develop suitable tests for the standardization of all OTC timed-release CCABA products. The Panel recommends that 4 years be provided for the development of such testing procedures. The Panel is concerned, however, that in the interim some products would be marketed with timed-release claims which, due to poor formulations, would deliver unsafe or ineffective dosages of drugs to the consumer. To assure that safe and effective products are available to the consumer, the Panel recommends that, during this interim period while the drug industry is developing standards with the Food and Drug Administration, sustained-release claims not be permitted in the labeling unless data have been presented before marketing to the Food and Drug Administration documenting that the timed-release preparation exceeds the single therapeutic dosage by an amount sufficient to produce blood levels or other effects that approximate those achieved by multiple administration of single therapeutic dosage units at accepted intervals based on the absorption and/or excretion characteristics of the drug.

The Panel is concerned that after reviewing the safety and effectiveness of active ingredients, a timed-release formulation may modify the safety and ef-

fectiveness in such a way that in essence these products will not be as safe or as effective as the Panel intends.

Any active ingredients or combination of active ingredients that include a claim for time-release will therefore be placed in Category III unless appropriate data can be presented to the Food and Drug Administration as outlined above.

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F. DEFERRAL OF "SORE THROAT" CLAIM

The term "sore throat" is used by consumers to describe a symptom frequently accompanying cough, nasal congestion, or the symptom complex of the "common cold." Sore throat appears as an indication or claim for a variety of products included in submissions reviewed by the Panel.

Ingredients to which sore throat indications and claims are attributed include, in general, local anesthetics and antibacterials. The Panel, working in conjunction with the Food and Drug Administration, has determined that the expertise for evaluating these ingredients for safety and effectiveness resides in the OTC Oral Cavity Panel and has therefore referred these ingredients and the "sore throat" indication and claim to the Oral Cavity Panel.

The Panel notes, however, that while the sore throat may be due to simple irritation resulting from nasal congestion and consequent breathing through the mouth, it may also be due to an infection with potential for serious complications. In the latter circumstances, the patient should not self-medicate and suppress the pain of a sore throat because delay in obtaining medical attention can have serious consequences. Labeling for products intended for relief of sore throat should emphasize that such products are for use only for "minor throat irritation." The products should bear adequate warnings that they are not intended for persistent or chronic sore throat accompanied by fever or other symptoms like headache, rash, nausea or vomiting, or glandular swelling. Labeling should also indicate the potential seriousness of a sore throat and bear adequate instructions for obtaining medical consultation.

G. DRUG MISUSE AND ABUSE

Drug abuse, in its broadest sense, can be described as intentional consumption of a drug for reasons other than legitimate therapeutic uses, often in excess of normally acceptable doses and dosage intervals. Drug misuse generally refers to overuse of a drug for therapeutic purposes due to misinformation or ignorance about its rational use. To the extent that OTC drugs are able to suppress symptoms and through their pharmacological actions also affect other systems to produce overtly perceived effects, i.e., side effects, misuse and/or abuse of OTC products can be expected to occur. The Panel believes, however, that drugs having documented effectiveness, therapeutic utility, and safety when used prudently for self-diagnosable conditions in accordance with label instructions represent a valuable, national public health resource.

Misuse and abuse of drugs is an increasing problem in our society. The Panel is aware of this problem and has addressed it to a limited extent. Of those drugs reviewed by this Panel, the formerly exempt narcotics listed in Schedule V (21 CFR 1308.15), alcohol, sympathomimetics, and belladonna alkaloids appear to be most subject to abuse. It is not within the purview or charge to the Panel to evaluate the numerous psychological, sociological, or economic factors involved in drug abuse. Consequently, the following comments and recommendations are based on medical and scientific data related to safety and effectiveness of these OTC drugs.

The risk of misuse and/or abuse is minimized by restriction on the types of pharmacologic agents in available OTC products, limitations on dosage and concentration of active drug, and adequate and explicit directions for use coupled with appropriate warnings. The Panel also urges that all appropriate measures be directed to reducing the incidence and severity of accidental overdosage, including increased education of the consumer regarding storage of medications, limitations on dosage units per product packages, and employment of safety packaging.

In general, OTC products that have been carefully formulated, thoroughly tested, and adequately labeled are safe when taken in accordance with label instructions for use and dosage. However, when these products are misused or abused, they may have unusual, unexpected, and/or toxic effects. Such drug abuse affects not only the individual himself, but society as a whole. The drug abuse problem is a complex one requiring the joint effort for solution by health care professionals, government, industry, educational institutions, and consumers.

The Panel urges for a balance in educational programs directed to consumers, which illustrate not only the horrors of narcotic addiction, but also the beneficial properties of effective therapeutic agents, their contribution to man's well-being, their undesirable side effects as well as the dangers inherent in all drugs if not properly used. The Panel believes prevention to be the key to the solution of drug misuse and abuse problems, and education to be the key to prevention. Because of the progressive nature of involvement with drugs, it is mandatory that groundwork in drug abuse prevention be laid down for children at an early age and reinforced throughout their lifetime.

There is, at this time, a conspicuous lack of data available on the nature and extent of misuse and abuse of OTC products. The Panel believes it is an obligation of the industry, government, and health care professionals to find out how these products, and especially potentially abusable ones, are being used and misused. The Panel recognizes a need for and recommends attention be directed to definitive, properly conducted studies to provide an indication of the magnitude and severity of the problem attendant to misuse and abuse of OTC products, especially those affecting the central nervous system.

1. *Codeine abuse.* During the time the Panel was in session, the Food and Drug Administration issued a proposed regulation in the FEDERAL REGISTER of September 12, 1972 (37 FR 18741) which proposed to place codeine-containing cough preparations on prescription by modification of 21 CFR 329.20.

At the present time, codeine-containing cough syrups are available for purchase OTC after the patient has signed a registry which records the consumer's name, amount purchased, intended use, and date of purchase. The proposed regulation would have restricted the availability of codeine-containing cough preparations, making such preparations available only by a physician's prescription.

At the request of the Food and Drug Administration, the Panel reviewed the studies on the basis of which the Bureau of Narcotics and Dangerous Drugs (BNDD) (now the Drug Enforcement Administration) asked the Food and Drug Administration to revoke the OTC status and discussed these studies with representatives of the BNDD. In addition, the Panel discussed the potential for codeine abuse with representatives from Food and Drug Administration's Division of Neuropharmacologic Drug Products and discussed with Food and Drug Administration officials aspects of the national policy concerning opium products and production.

This policy was related to the need to reduce illicit drug traffic in narcotics by reducing national imports of opium. A high percentage of imported opium is processed to produce codeine, which is used in codeine-containing OTC cough

preparations. By placing these preparations in a "prescription only" category, their use would be severely reduced and thus the nation's need for imported opium reduced. In addition, BNDD had performed several studies that seemed to indicate a high incidence of abuse of codeine-containing cough preparations, possibly leading to drug addiction and contributing to the illicite drug traffic.

After review of all pertinent scientific data, the Panel concluded that codeine and its salts are safe and effective for OTC use as antitussives when used in accordance with instructions on the label. The potential for abuse of codeine is viewed by the Panel as negligible. When taken by mouth, codeine rarely causes physical dependence. Although codeine can partially suppress morphine withdrawal, it may require high doses in the range of 1,200 to 1,800 mg per day given by injection.

The Panel forwarded to the Commissioner the following statement:

> Deliberations of the Panel have resulted in a statement that codeine is safe and effective for OTC use as a cough suppressant. It is further the opinion of the Panel that under usual conditions of therapeutic use, codeine has low dependence liability. On the basis of scientific and medical evidence alone, it is the Panel's opinion that codeine-containing cough suppressant preparations should continue to be available over-the-counter. The Panel recognizes, however, that in the matter now pending before the Food and Drug Administration (removal of prescription exemption for such preparations), considerations go beyond questions of safety and effectiveness alone. The Panel does not deem it part of its function to evaluate factors which are not directly concerned with medical safety and effectiveness. Because there appears to be a conflict between the findings regarding the basic safety and effectiveness of codeine and the removal of the prescription exemption, the Panel strongly urges that FDA clearly identify all factors which lead to FDA's final decision.

As a result, the Commissioner issued a notice withdrawing this proposal in the FEDERAL REGISTER of March 24, 1975 (40 FR 12998), thus retaining codeine-containing cough preparations on OTC status.

2. *Alcohol abuse.* Alcohol, in concentrations up to 42 percent, i.e., 84 proof, is present as a vehicle in a variety of OTC products reviewed by the Panel.

The Panel recognizes a potential for abuse of alcohol contained in OTC cold, cough, allergy, bronchodilator, and antiasthmatic products and recommendations directed to educational programs and need for studies to determine the incidence and severity of misuse and abuse of drugs apply equally to abuse and misuse of alcohol.

H. PEDIATRIC DOSAGE

The Panel is aware that data on the use in children of most drugs in CCABA products are negligible or nonexistent. Yet, pediatric patients comprise a substantial proportion of the population that receives these OTC products.

The dosage that will produce optimum therapeutic effects in a particular patient, adult or child, is dependent upon factors such as the drug itself, individual patient variables such as special sensitivity or tolerance to the specific agent, age, weight and metabolic, pathological, or psychological conditions. Children's dosage calculated by any method that does not take all of these variables into account, therefore, can only be considered general guides.

Definitive pediatric drug dosage should be derived from data obtained in clinical trials with children using protocols similar to those used in adult patients. The Panel recognizes the extreme difficulties attendant upon such trials but also recognizes the immediate need to make recommendations for pediatric dosage pending availability of such definitive data.

Traditionally, pediatric dosage calculations for infants and children have been based on body surface area, weight, or age of the child as a proportion of the "usual adult dose." Dosage calculated on the basis of the age of the child, although convenient, may be the least reliable method because of the large variation in the weight of patients at a specific age. However, for OTC products that have a relatively wide margin of safety, the Panel has concluded that dosage recommendations based on age are the most reasonable since they would be most easily understood by the consumer.

In order to provide the needed dosage recommendations for pediatric patients, the Panel sought the assistance of a panel of experts in pediatric drug therapy. This Special Panel on Pediatric Dosage was convened and met concurrently with this Panel on October 31 and November 1, 1974 and made recommendations. Members of the Pediatric Panel were:

Charles Janeway, M.D.
Sumner Yaffee, M.D.
Jennifer Loggie, M.D., B. Ch.
C. Warren Bierman, M.D.
Louie G. Linarelli, M.D.
Vincent D. Larkin, M.D.
Constantine Falliers, M.D.

Subsequently, the Special Panel on Pediatric Dosage conducted correspondence and review of all pediatric dosage recommendations. These recommendations have been considered in the preparation of this document.

Unless indicated contrarily, the Panel recommends the following guidelines for determining safe and effective pediatric dosages for the individual CCABA ingredients discussed in this document: For infants under 2 years of age, the pediatric dosage should be established by a physician. For children 2 to under 6 years of age, the pediatric dosage is ¼ the adult dosage; for children 6 to under 12 years of age, the dosage is ½ the adult dosage.

The Panel has determined that the labeling terms "baby" and/or "infant" on CCABA products implies that such products have been approved for use in children under 2 years of age. The Panel, therefore, concludes that CCABA products exclude from their labeling the imprecise terms "baby" and/or "infant" unless the ingredient(s) has been specifically demonstrated as safe and effective for children under 2 years of age. In addition, products shown to be safe and effective for children under 2 years of age must provide specific dosages in their labeling for that indication(s). Products with labeling claims for children under 2 years of age not shown to be safe and effective for that age group are considered Category II.

The differences between children under 2 years of age, and other age groups with respect to the anatomy and physiology disorders of their respiratory system, their responses to diseases affecting the respiratory system, and their responses to drugs make general labeling restrictions for this age group essential. For example, infants because of the smaller diameter of their respiratory airways are particularly prone to the complications of respiratory distress during an acute respiratory tract infection such as may occur in the "common cold." Therefore, parents of children under 2 years of age should be advised to consult a physician for diagnosis and individualized therapeutic recommendations, even for symptoms and conditions that are considered appropriate for self-medication in older children and adults. Because of these considerations, the Panel recommends that the general labeling of CCABA products for use in children under 2 years of age requires the advice and supervision of a physician.

The Panel concurs with accepted medical practice that recommends that children be administered a minimum amount or no alcohol. Therefore, alcohol in pediatric formulations should be maintained at the lowest possible concentration. If pharmaceutically possible, products should be formulated without alcohol. Therefore, the Panel recommends that CCABA products containing an alcoholic content greater than 10 percent (weight/weight) should not be given to children under 6 years except under the advice and supervision of a physician.

In the recommendation of the Special Panel on Pediatric Dosage, restrictions on the use of certain drugs were made because of the lack of data and/or experience in the pediatric population. Some drugs may be restricted because of the need for a physician's examination and evaluation of the medical problem for which a drug may be indicated. Still other drugs are not recommended for use in children because of inherent drug toxicity in the pediatric age group. This Panel will indicate, where applicable, pediatric dosages, limits, or warnings, in its discussion below of individual ingredients.

I. INACTIVE INGREDIENTS

A variety of inactive ingredients is used in the manufacture and formulation of products reviewed by the Panel. Such ingredients are intended as flavoring agents, aromatics, vehicles, colorants, sweeteners, etc.

Although the Panel did not review these inactive ingredients, it is the view of the Panel that their safety and the advisability of including them in drug products be reviewed by an appropriate body. Since many of these ingredients are used in the formulation of many drug

products other than those reviewed by this Panel, it is not appropriate that they be dealt with specifically and solely in relation to CCABA products.

For various reasons, individuals may wish to avoid using certain inactive ingredients found in drug products. These reasons may be allergic reactions, idiosyncratic responses, fear of safety (whether valid or not), or personal dislike. It is impossible to make a free choice in this regard unless the full contents of drug products are listed on the label. Therefore, this Panel strongly recommends that the Food and Drug Administration require full ingredient labeling of inactive as well as active ingredients in descending order of quantities present in all drug products. In support of this position the Panel notes that food products are already required to have such labeling, and since the purpose of a drug is to alleviate symptoms of disease, it would seem much more compelling to have this information on all drugs.

In line with the Panel's desire to expose the consumer to the smallest number of ingredients possible, the Panel has previously recommended that marketed products contain only those ingredients essential to the product. (See part II. paragraph C.2. above—Limitation of Ingredients in Combination Products.)

Although chloroform was reviewed, and considered by the Panel to be an inactive ingredient, it was reviewed again at the special request of the Food and Drug Administration, because of reports suggesting that it is carcinogenic (Refs. 1 and 2). A discussion can be found later in this document. (See part IV. paragraph B.2.b. below—Chloroform.)

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(2) OTC Volume 040338.

J. ADVANTAGES OF SINGLE INGREDIENT PRODUCTS

OTC drug combination products seem to provide the public with many options from which to select the preparation most likely to relieve a symptom or group of symptoms. The combinations available would seem on the surface to be rational. The Panel has discussed CCABA combination products earlier in this document. (See part II. paragraph C.1. above—General combination policy.) However, the individual may need or tolerate only one of the ingredients in the combination product and the presence of the others may be unnecessary or, because of side effects or idiosyncratic reactions, their presence may preclude use of the combination.

Great variability with regard to side effects induced by drugs is seen among patients. Common examples are drowsiness caused by antihistamines and nervousness and sleeplessness caused by ephedrine. Furthermore, the ratio in which the components exist in the combination will be unsuitable for some persons. Although these effects and the drugs producing them are familiar to physicians and pharmacists, the public is unlikely to identify the ingredient causing the side-effect if the ingredient is present in a combination. This difficulty is largely avoided with single ingredients, which many physicians prefer to prescribe. With a single ingredient, whether available OTC or on prescription only, the patient can recognize the drug's action with relative ease and can adjust the dosage according to need. Experience gained in this way could be very useful to the patient on occasions of future need for self medication.

Single ingredients are rarely available among CCABA OTC drugs. Since many physicians prefer to treat with single ingredients, it seems logical for the public to have the option to medicate themselves with single ingredients also.

In summary, availability of individual ingredients would provide increased opportunity for the public to evaluate OTC drugs and allow the public to avoid taking two or more drugs where one might suffice. This will promote more specific and possibly safer self-medication.

It is strongly recommended therefore, that any active ingredient marketed in OTC preparations for cold, cough, etc. be equally available OTC as a single ingredient and in a form equally convenient to administer.

K. ADVERTISING

The Panel is aware that the role of the Food and Drug Administration is to regulate labeling of over-the-counter drugs and the role of the Federal Trade Commission is to enforce adherence to such labeling in advertising. In addition to recommending specific labeling claims, warnings, and dosages, the Panel would like to make some general comments and recommendations regarding advertising of drugs.

Advertisements extend the label beyond the pharmaceutical counter or medicine cabinet. The public may well receive most of its attitude toward CCABA remedies from advertisements—particularly television advertisements.

For this reason the Panel strongly urges the Federal Trade Commission to challenge any advertisement which:

1. In any way negates or dilutes the information on the label, especially the contraindications and/or warnings;

2. Suggests or leans heavily on words, phrases, and portrayals that lead the lay person to assume that the product is to be used in any manner not recommended in the monograph established below, or that it cures when in reality it only alleviates symptoms.

The Panel further recommends that advertisements for CCABA remedies not be placed where they can promote or suggest use by children, and if such an advertisement is placed where numbers of children may learn of the indications for the product, that such advertisement contain clear and specific warnings and contraindications concerning child use.

L. STATEMENT ON CCABA COMBINATION PRODUCTS CONTAINING ASPIRIN

The Panel is aware that certain individuals develop manifestations simulating an allergic reaction within 15 to 45 minutes after taking 300 to 600 mg of aspirin (acetylsalicylic acid) (Ref. 1). Such reactions may occur even though aspirin has previously been well tolerated by these individuals for many years. The major manifestation of such an allergic type reaction to aspirin is asthma, which may be of such severity as to be life-threatening. These manifestations are those seen in acute allergic reactions. Other manifestations include intense nasal stuffiness and urticaria. However, all efforts to demonstrate an allergic mechanism to account for these reactions have failed.

In a study of nine analgesic drugs with respect to their capacity to induce bronchial reactions in aspirin-sensitive asthmatic patients and their ability to inhibit prostaglandin synthetase activity, those five drugs (aspirin, indomethacin mefenamic acid, flufenamic acid, and phenylbutazone) active in causing asthma were also active in inhibiting the enzymes (Ref. 2). Of the nine analgesics, four drugs (salicylamide, paracetamol, benzydamine, and chloroquine) lacking the capacity to induce asthma on challenge in aspirin-sensitive asthmatic patients also lacked the capacity to inhibit prostaglandin synthetase activity. Since some prostaglandins have bronchoconstrictor activity whereas others have bronchodilator activity, it was postulated that aspirin and other drugs giving asthma on challenge may do so by modifying prostaglandin synthesis. Inhibitors of prostaglandin biosynthesis such as aspirin should not be given to patients with aspirin-sensitive asthma (Ref. 2).

The available clinical evidence indicates that the presence of the acetyl group in aspirin is essential for such reactions to occur since sodium salicylate and other salicylates are well tolerated in aspirin-sensitive persons.

The frequency of adverse reactions to aspirin among asthmatic children 6 to 16 years of age is reported to be 1.9 percent (Ref. 3), and among adult asthmatics the reported frequency exceeds 3 percent and may be substantially higher (Refs. 1, 4, 5, and 6). There are at least two reports of death following the ingestion of aspirin (Refs. 7 and 8). Asthma may appear for the first time, after taking aspirin, in individuals who may have previously tolerated aspirin. Therefore, the Panel feels that a warning limited to the statement that aspirin-containing preparations be avoided by those with already existing asthma would be inadequate.

A common history in individuals who previously tolerated aspirin is long-standing perennial rhinitis, chiefly characterized by nasal stuffiness. Nasal polyps are very common but are not invariably present. Asthma may or may not have been present. The Panel is concerned that individuals having tolerated aspirin in the past may develop a severe reaction, usually an asthmatic attack, following the taking of a CCABA product containing aspirin. If aspirin is present in a combination drug product, aspirin is usually not recognized as the cause of

the reaction until such episodes occur once or twice more.

The association between nasal polyps, asthma, and aspirin sensitivity has been recognized for many years, and there are many reports in the literature (Refs. 1, 3, and 9). Eosinophilia is the rule in these patients and this should be considered as part of the syndrome. The yellow dye, tartrazine, and the anti-inflammatory drug, indomethacin, are also reported to cause asthma in these patients (Ref. 9).

The Panel recognizes that prevention is the logical course, which includes recognition of the syndrome and proper instruction given to the patient. However, the Panel notes that the presence of aspirin in combination with other drugs can lead to ingestion of aspirin by error, a point frequently made by patients. Furthermore, the first reaction of this kind in aspirin-sensitive individuals will often go unrecognized if aspirin is in combination with other drugs. For this reason the Panel concludes that the availability of aspirin in combination drug products can be expected to lead to more of these severe reactions than would occur if aspirin were only available as a single ingredient.

The OTC drugs under review by the Panel are frequently taken by consumers in whom reactions to aspirin are most frequent. The Panel notes that other analgesics like acetaminophen are available and may be included in specific combination products. (See part II. paragraph C. above—Principles Applicable to Combination Products.) For this reason, the Panel concludes that CCABA combination products containing aspirin (acetylsalicylic acid) should be labeled under the heading *"Warning":* "This product contains aspirin and should not be taken by individuals who are sensitive to aspirin."

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M. GENERAL STATEMENTS ON THE DETERMINATION OF SAFETY AND EFFECTIVENESS FOR CCABA PRODUCTS

1. *Determination of safety.* a. *Single drugs.* In deciding on the safety of a drug or combination of drugs, both animal and human studies were considered.

Although animal studies were of interest, they were seldom very helpful because it would be unusual for a drug to reach the market without satisfactory animal safety data. The animal data usually related to levels of the drug that might cause death and the effect of the drug on various organs such as the bone marrow, liver, and kidneys.

Major attention was paid to information related to adverse effects in humans, both adults and children. A knowledge of the pharmacology of the drug or drugs under consideration made it possible to look specifically for adverse effects in one or more systems. It was important that there be studies in which the drug was compared with a placebo. In addition, blood levels related to toxic effects were very useful and could be related to various dosages and routes of administration. Examples of the great variety of possible toxic effects are as follows:

(1) An adverse effect might be present but this might not be very serious and could be dealt with by careful labeling, e.g., the drowsiness caused by many antihistamine drugs.

(2) A drug might have abuse potential. For example, the abuse potential for codeine was considered small, but the abuse potential for stramonium was considered very high.

(3) The effect of repeated doses of the drug had to be considered, e.g., the rebound nasal congestion which can occur with repeated doses of nasal decongestant drops or sprays.

(4) A possible excessive therapeutic effect was considered, e.g., the drying effect of drugs from different pharmacologic groups (antihistamines and anticholinergics) on the bronchial tree.

(5) The possible depressant effect other than that related to the symptom under consideration, e.g., a cerebral depressant effect of an antitussive.

(6) The route of administration of drugs had to be considered, for example, the local effect on the bronchial tree of drugs used in the treatment of asthma where these were administered in an aerosol. Another example is the use of suppositories of theophylline that could be additive to theophylline given by mouth.

(7) The seriousness and frequency of known idiosyncratic reactions might be critical, e.g., the very serious adverse effects of aspirin in some patients with asthma.

(8) There might be interactions with other drugs such as the serious result of taking ephedrine with a monoamine oxidase inhibitor which would cause a severe rise in blood pressure.

All the above were considered, and in addition, information was sought regarding any differences that might occur when the drugs were given to children of various ages as compared with adults. Children less than 1 year tend to metabolize drugs differently from older children and, as this was difficult to predict, this was one factor leading to the decision of the Panel not to label drugs for OTC use in children under 2 years except under the advice and supervision of a physician. (See part II. paragraph H. above—Pediatric Dosage.)

The importance of clear labeling of warnings and cautions was continually considered, and it is recommended that the public be educated to read labels carefully and to take the warnings and cautions seriously.

b. *Drug interactions.* There is little, if any, documentation of drug interactions between OTC drug products or between OTC drug products and prescription products and only speculation can be offered regarding such potential interactions. Even well-documented drug interactions may depend on drug dosage levels not usually attained with OTC products. Therefore, in considering the safety of OTC drugs, one must consider not only possible effects of single drugs but also possible adverse effects of interactions between drug combinations. The Panel has recommended appropriate labeling warnings where there are serious concerns.

2. *Determination of effectiveness.* In determining effectiveness, it was necessary to consider each pharmacologic group separately although certain general principles applies to all groups.

Animal studies were seldom very helpful except in the case of antihistamines where one of the requirements for efficacy was the capacity of the drug to decrease or suppress anaphylaxis and the effects produced by histamine in animals.

Major attention was paid to clinical studies especially where the double-blind technique could be employed. In some situations the ability to do a crossover study was of additional value. Studies in which there were objective measurements with proper controls and statistical analysis were of considerable weight in the Panel's decision to place an ingredient in Category I. However, certain drug actions made such objective measurements extremely difficult or impossible and therefore, large well-controlled subjective studies were considered of reasonable use. Partially controlled and uncontrolled clinical studies were of very limited value but both were considered by the Panel. Clinical experience of a general nature, if documented by qualified experts, added somewhat to the final decision. It was considered particularly useful if similar results were obtained.

In some instances, the Panel considered the Drug Efficacy Study data. The Drug Efficacy Study of the National Academy of Sciences—National Research Council (NAS/NRC) reviewed the data submitted to the Food and Drug Administration to support effectiveness of only marketed products that had re-

ceived premarket clearance through a New Drug Application (NDA) for safety prior to 1962. The Panel in reaching its decision considered all the studies available including information from the Drug Efficacy Study.

Examples of the different types of studies (all of which should be placebo controlled) used by the Panel to assess different drug groups are as follows:

a. Antitussives are best assessed by objective cough-counting techniques. The antitussive can be tested by decreasing induced cough or by decreasing the cough in patients with chronic cough.

b. Expectorants may be assessed by large double-blind crossover subjective studies in patients with chronic lung disease or randomized double-blind studies in patients with acute upper respiratory infections. These studies are acceptable because objective techniques for assessing the expectorant action of a drug are not yet satisfactory and require further development.

c. Bronchodilators are best assessed by objective measurements of pulmonary function in asthmatics where a significant improvement in pulmonary function can be shown after the use of the drug.

d. Antihistamines require the study of large groups of patients with strict double-blind control using a subjective evaluation of the effect of the drug on allergic rhinitis or on the symptoms of the "common cold". These clinical subjective studies are acceptable as there is no definite objective technique for measuring the effect of antihistamines in these conditions. Anticholinergic drugs which are used in the treatment of rhinitis with rhinorrhea require clinical testing similar to that of the antihistamines.

e. Nasal decongestants which relieve obstruction to the nasal passages are best assessed by objective measurements of resistance to air flow through the nose. In this way comparisons of the drug and the placebo can be made using data of airway resistance measurements.

Although all the evidence related to the effectiveness of a drug was considered, the above studies in the various pharmacologic groups had the greatest influence in determining a Category I classification.

It was extremely difficult to judge the effectiveness of combinations of ingredients because of the many different dosages involved and the difficulty in determining the effect of each individual ingredient in the combination. The Panel considered it reasonable that Category I ingredients from different pharmacologic groups differed sufficiently from one another to reduce the likelihood of a competitive or potentiating effect between ingredients, and their combination was therefore considered effective. There are some exceptions to this and these exceptions are discussed in the section on combination drugs. (See part II, paragraph C.—Principles Applicable to Combination Products.)

To assist in the testing of ingredients in the future, the Panel developed clinical testing procedures for each pharmacologic group. These procedures have been included in the "Data Required for Evaluation" sections following the ingredient(s) statements for each pharmacologic group.

N. AEROSOL DOSAGE FORMS OF DRUGS UTILIZED IN CCABA PRODUCTS

The utilization of the pressurized, self-contained and self-propelled "aerosol" dosage forms in delivering pharmaceuticals was begun in the 1950's when advances in the technologies of propellants, valves, and containers made possible the accurate delivery of metered doses for direct inhalation into the respiratory system. Development in the areas of fine particle technology and different aerosol systems kept pace with the evolution of specialized valves and actuators, containers of diverse materials such as glass, coated metals and plastics, and a variety of propellant gases such as the halocarbons, compressed gases (nitrogen, carbon dioxide, nitrous oxide), and hydrocarbon gases (butane, isobutane, pentane).

The Panel is aware of the advantages and disadvantages of the pressurized drug products that were the subject of submissions to the Panel.

Among the advantages may be listed:

1. Aerosol products are permanently sealed units, and thus their contents are maintained in a stable form that is protected from accidental contamination by organisms, atmospheric gases, moisture, and sunlight that are sometimes encountered with the use of ordinary containers that are repeatedly opened.

2. The utilization of specialized valves and adapters permit the release of mists, sprays, or true aerosols (particles suspended in gas), in a controlled manner that assures the rapid administration of the aerosolized drug. This is particularly useful when prompt onset of action is desirable.

3. Metering valves and containers are available in compact form, so as to permit the consumer to carry the product on his person with little inconvenience and with quick accessibility when medication is required.

4. Aerosol products designed to emit an intermittent or continuous spray of medicaments into the atmosphere of a room are capable of producing aerosolized mists containing particles that are fine enough to be inhaled and thus exert their effect rapidly in the respiratory tract.

In recent years the advantages of the aerosolized forms of drugs for treatment of bronchial asthma and the transitory symptoms of the "common cold" have been challenged because of potential toxicities. These include the cardiotoxicity potential of the halocarbon propellent, fluorocarbon 11. Several studies have been reported that indicate that the propellant can be absorbed into the blood with a persistence of a small quantity in the blood after 1 hour.

Reports of accidental sudden deaths following the inhalation of aerosols emptied into a plastic bag indicate an abuse potential that cannot be overlooked.

More recently predictions based on the use of computer models have warned about the possibility that halocarbons released into the air from aerosol products may be the cause of depletion of the ozone layer in the stratosphere. Concern has been expressed that if these predictions are accurate then the protective elements of the stratosphere against ultraviolet radiation may become impaired.

The Panel, therefore, concludes that although aerosol products do possess inherent advantages for specialized application of drugs in bronchial asthma and other respiratory conditions, the possibility of toxic effects of the halocarbon propellants should be carefully evaluated by a suitable Panel of experts in this area.

O. CCABA PRODUCT LABELING CLAIMS NOT SUPPORTED BY SCIENTIFIC EVIDENCE

The Panel has reviewed the submitted labeling claims made for CCABA products. It is interesting to note that products sold for relief of symptoms of the "common cold" and allergies are probably the largest category of OTC drug products on the United States OTC drug market. In fact, there are estimates by the Food and Drug Administration that as many as 50,000 different OTC CCABA drug products are currently marketed. Because of this vast array of products, the consumer is often faced with a myriad of confusing claims, which are not only vague and hard to comprehend, but also make it almost impossible for the consumer to distinguish between these products.

One of the primary functions of this Panel is to minimize this confusion by clarifying the labeling. In that way the ordinary individual who purchases an OTC drug product for the relief of symptoms, e.g., of the "common cold" or allergies, will understand exactly what the product will do for him, the limits of the product's capability, and the cautions to be observed when using that product. It is also a basic function of the Panel to attempt to reduce confusing labeling claims to a reasonably concise number of understandable claims, permitting the consumer to easily distinguish between various CCABA products. The Panel believes that at the present time this is not possible since the labeling that appears on many currently marketed CCABA products tends to be overly complicated, vague, unsupported by scientific data, and in some cases is false and misleading.

The Panel understands the drug industry's desire to market OTC drug products for the relief of symptoms of the "common cold" or allergies by suggesting uniqueness or superiority of one product over another. But uniqueness or superiority must be proven scientifically or labeling will mislead and unduly confuse the consumer. For example, if one ingredient can be demonstrated to be superior to another because of greater effectiveness, then the consumer should be so informed. Conversely, if two ingredients are indistinguishable with regard to effectiveness, e.g., both are equally

effective in suppression of cough, then it is misleading to claim superiority for one of the ingredients. In this regard, the Panel wishes to make clear that its function is not to compare various ingredients in order to determine the OTC drug of choice. Rather, the Panel determines only safety and effectiveness for active OTC CCABA ingredients, as well as proper dosage ranges for OTC drug use. In reviewing the scientific literature for CCABA ingredients, it is clear that ingredients of the same pharmacologic group that are Category I, i.e., generally recognized as safe and effective, have similar effectiveness in the dosage ranges recommended. Consequently, the Panel concludes that all claims which imply superiority of one product over another, both of which contain Category I ingredients in the same pharmacological group, should be prohibited from the labeling of CCABA products. These claims would include such phrases as "Superior to ordinary" and "Specially improved or selected ingredients".

In addition, the Panel has determined that statements alluding to superiority due to greater potency, such as "extra strength" or "contains more active ingredient per dose", are also misleading unless fully documented. The Panel can find no justification for claiming more activity per dose for one Category I ingredient over another because there is no scientific merit from a therapeutic point of view between a product containing 15 mg of a drug A and another containing 30 mg of drug B if they are similarly effective. Unsubstantiated claims for "extra strength" or "contains more active ingredient per dose" or "higher dose level" or "stronger than" are therefore misleading. However, assuming that claims of greater potency were based on documented facts, such increase in potency might also indicate an increase in the potential side effects. Under such circumstances the Panel feels that such claims are misleading to the consumer.

Misleading superiority claims may also manifest themselves as claims that state or imply actions peculiar to a particular product, when in fact those claims are applicable to all OTC drug products or all Category I ingredients of the same pharmacologic group. Thus, for example, if two different OTC cough products contain different Category I antitussive ingredients, it would be misleading to make such claims as "specially formulated" or "specially selected ingredients". This view would, of course, also be applicable to combinations of appropriate CCABA ingredients or combinations of CCABA and non-CCABA ingredients. Thus, claims such as "teamed components" would also be considered misleading by the Panel.

Another area of concern to the Panel is claims implying a unique physiological action that either has no scientific foundation or meaning or that will be meaningless to the consumer. Such claims include pseudo-medical terms such as "antiallergic", or pseudo-medical activities such as "gets at the roots of", "fights", "wakes up", and "multiaction". Some claims mislead the consumer into believing a product has a unique action, when in fact that pharmacologic action is shared by all similar OTC drug products containing active ingredients from the same pharmacologic class. Examples include claims that an ingredient "travels through the bloodstream" or "works internally". All drugs taken internally "work internally" and virtually all drugs taken internally are absorbed into the bloodstream. Thus, these claims are also not appropriate in OTC labeling.

Finally, the Panel is concerned about vague generalizations relating to time that do not actually relate to the directions or indications. This is especially true where the time stated in the claim is indeterminate. Thus, claims such as "fast" and "prompt" should not appear on labels unless they are directly correlated to the directions for use permitted in the monograph.

P. CCABA PRODUCT NAMES AND LABELING CLAIMS ASSOCIATED WITH DISEASES AND RELATED SYMPTOMS

The Panel has made a clear distinction in this document between the treatment for the relief of the symptoms of a disease, e.g., cough, runny nose, and the treatment of the disease itself, e.g., "common cold." With few exceptions, CCABA products are indicated only for the treatment for the relief of symptoms. The most common disease associated with CCABA products is the "common cold." The Panel has discussed this respiratory disease earlier in this document. (See part II. paragraph B.3. above—The "common cold.") The Panel concludes that there is no demonstrated safe and effective OTC active ingredient or combination of active ingredients acceptable for specific treatment of the "common cold." Consequently, the Panel recommends that product names or labeling claims that infer or suggest a direct relationship to the "common cold," e.g., "cold medicine," "cold formula," "for relief of colds," should not be allowed. Such statements may mislead the consumer into believing that these products prevent, treat, or cure the disease itself.

The active ingredients reviewed by the Panel and included in currently marketed CCABA products are generally used for the treatment or relief of the symptoms of disease. The Panel concludes that if labeling is restricted to the proven pharmacologic activities of the active ingredients in CCABA products, reference in labeling to the specific activities of such ingredients in alleviating symptoms is acceptable. The Panel has summarized the commonly encountered symptoms and the acceptable pharmacologic groups earlier in this document. (See part II. paragraph B. above—Diseases and Related Symptoms Relieved by OTC Cold, Cough, Bronchodilator and Antiasthmatic Products.)

For drugs used to treat the symptoms of the "common cold," the Panel recommends that in addition to the acceptable claims (Category I) for specific pharmacologic groups, the following phrases may be used: "(symptoms) as may be associated with the 'common cold' " or "as may occur in the 'common cold' ". An example for a product containing an antitussive would be "For cough as may occur in the 'common cold'."

On the other hand, the Panel finds that certain OTC bronchodilator active ingredients are safe and effective for the treatment of asthma. This disease is effectively treated by OTC products but requires prior diagnosis of asthma by a physician. Bronchodilators serve to relieve the primary manifestations of asthma, shortness of breath, which is caused by widespread narrowing of the airways due to airway wall muscle spasm. The Panel recognizes that bronchodilators cannot prevent or cure the disease but are effective in relieving the primary symptoms. Because of these unique symptoms and because the Panel believes these products should be easily identifiable and accessible to those afflicted with the disease, the Panel concludes that use of the term "asthma" in labeling of products containing Category I bronchodilator active ingredients, either as part of a product name, e.g., "asthma medicine", or appearing alone in labeling claims, e.g., "treatment of asthma", is acceptable. The Panel is of the opinion that reference to asthma in labeling is not misleading and further, is essential for those individuals diagnosed by a physician as having the disease. This of course is acceptable, based upon the Panel's recommendation later in this document that the following warning be on all products containing bronchodilators: "Do not use this product unless a diagnosis of asthma has been made by a physician". (See part V. paragraph B.1. below—Category I Labeling.)

The Panel also recognizes that allergic rhinitis (such as hay fever) is a very common disease. Unlike the "common cold," most affected individuals understand the etiology of such a disease and realize that it cannot be prevented or cured by OTC antihistamines or nasal decongestants. However, as was the case with asthma, the manifestations of this disease can be treated with such a product. Here again, it is the Panel's conclusion that it is also acceptable for the terms "hay fever", and "allergic rhinitis", to appear in labeling of products containing Category I ingredients either as part of a product name, e.g., hay fever medicine, or appearing alone in labeling claims, e.g., "Dries running nose as may occur with allergic rhinitis", or "For treatment of hay fever".

Q. INGREDIENT EQUIVALENCE

The Panel recognizes that the ingredients submitted and reviewed may exist in chemical forms other than those considered in this document. The Panel notes that other salts, esters, and complexes of these ingredients may be available, which may be therapeutically equivalent to the forms of the ingredients considered by the Panel. In recognition of this fact, the Panel concludes that provided that there are suitable data to establish bioequivalence and safety, salts, esters, and complexes of ingredients dis-

cussed in the monograph would be acceptable. However, it is essential that the dosage used be equivalent to the dosage of the ingredient in the monograph.

INTRODUCTION TO PHARMACOLOGIC CLASSIFICATIONS

Not all CCABA products are used for the same purpose, nor should the requirements for effectiveness be the same. In an attempt to classify CCABA active ingredients and their products it was necessary to distinguish between the pharmacologic activities and resulting effectiveness for labeled claims of these products.

The following classifications of CCABA product ingredients was developed by the Panel in an attempt to simplify categorization of ingredients and thereby eliminate labeling confusion:

Antitussives
Expectorants
Bronchodilators
Anticholinergics
Antihistamines
Nasal decongestants
Miscellaneous active ingredients

III. ANTITUSSIVES

A. GENERAL DISCUSSION

An antitussive agent specifically inhibits or suppresses the act of coughing. Direct inhibtion may result from: depression of medullary or higher centers in the brain; diminishing the sensitivity of the cough receptors in the membranes lining the throat and respiratory passageway; interruption of the transmission of the cough impulses to the brain or to the muscles that are involved in the act of coughing; and by removal of irritants and excessive secretions through the improvement in bronchial drainage.

In theory, cough suppression may be produced indirectly by one of two mechanisms: A soothing action on the irritated or inflamed throat, which would in effect decrease the sensitivity of special nerve endings or cough receptors in such membranes; and a relief of spasm or localized constriction of the airway. This is known to occur in asthma or following the inhalation of an irritant.

The Panel has followed the presently accepted medical approach and has classified antitussives according to their principal site of action.

1. Centrally acting antitussive agents produce cough suppression by acting on the central nervous system to depress the medullary (brain) cough center and thus raise its threshold for afferent (incoming) cough impulses. These agents may be further subdivided into narcotic antitussives, such as codeine, and nonnarcotic antitussives such as dextromethorphan.

2. Peripherally acting antitussive agents act on the nerve receptors within the respiratory tract. Cough suppression may be produced by several different mechanisms such as a local anesthetic (pain deadening) or analgesic (pain suppressing) action on the mucosa of the respiratory tract; enhancing bronchial airway drainage by reducing the viscosity (thickness) of retained secretions, which may occur with effective expectorant agents or with adequate humidification of the airway; relaxation of the smooth muscle of the bronchial airway in the presence of spasm; or a soothing (demulcent) effect on the irritated throat and bronchial airway walls.

The narcotic antitussives have traditionally been the most effective agents available for suppressing cough. Because of its low abuse potential, codeine, the best known and most widely used antitussive in this group, has been considered safe for OTC use. Except in unusual circumstances in which cough is associated with pain, e.g., in pleurisy, the more potent narcotics such as morphine are not used because of their potential for acute toxicity from overdosage (respiratory depression) and abuse potential. Such drugs are best administered under medical supervision.

Nonnarcotic antitussives, such as dextromethorphan, act by selective suppression of the central cough mechanism and have no significant abuse liability. Therefore, they would seem to be more advantageous for use in treating cough and also for use in individuals who seem psychologically predisposed to drug dependence.

In general, the antitussives available for OTC use are and should be designed to diminish coughs associated with acute, self-limiting conditions that cause irritation to the respiratory airway. Since it is highly unlikely that such conditions would persist for more than 1 week, the Panel has limited the period of administration of these antitussives to a maximum of 7 days. A persistent cough for more than 1 week or one accompanied by high fever, rash, or persistent headache may be indicative of a serious disease, which should be treated by a physician and does not lend itself to self medication by antitussives. (See part II. paragraph B.4. above—Cough.) In asthma, bronchitis, pulmonary emphysema, and a number of other respiratory diseases, there is often an over production of secretions which accumulates in the airway and results in a cough productive of thick sputum. The suppression of cough by antitussives in such instances would impair clearing of the airway and could be harmful.

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Labeling

Consumers often have difficulty understanding the intended meaning of OTC drug labeling. The Panel concludes that use of vague words, or words which imply a greater effectiveness than other similar OTC products, is false and misleading. The Panel has reviewed the labeling that was submitted for antitussives and for other pharmacologic groups and has attempted to explain why some labeling is acceptable, objectionable, or questionable.

In the case of antitussives, the Panel has reviewed the symptoms of cough and the mechanisms by which the physiologic response is produced. Cough occurs in healthy individuals as a mechanism for clearing the airway of any obstructing mucus or inhaled foreign material. As indicated above, medications that suppress the act of coughing by reducing the number of coughs and/or the intensity of coughing are known as antitussive drugs. Based upon the previous discussion of cough and the discussion of antitussives, the Panel concludes that the following indications are acceptable labeling claims for generally recognized safe and effective antitussives (cough suppressants) for the temporary relief of cough: "Cough suppressant which temporarily reduces the impulse to cough". "For the temporary relief of coughs due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants". "Temporarily quiets coughing by its antitussive action". "Temporarly helps you cough less". "Temporarily helps to quiet the cough reflex that causes coughing".

Because of the lack of clinical studies in children under 2 years of age, the Panel was unable to determine an OTC dose for this age group. Based upon the lack of available data, the Panel recommends the following warning for products containing antitussives: "Do not give this product to children under 2 years except under the advice and supervision of a physician".

Since a persistent or chronic cough may be a sign of a serious condition requiring medical intervention and should be brought to the attention of a physician, the Panel recommends that all labeling for antitussive products bear the following warning: *"Caution:* A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur, or is accompanied by high fever, rash or persistent headache, consult a physician".

In asthma, bronchitis, pulmonary emphysema, and a number of other respiratory diseases, there is often an overproduction of secretions, which accumulate in the airways and results in a cough that produces thick mucus. The suppression of cough by antitussives in such instances would impair clearing of the airway and could be harmful; therefore, the Panel recommends the following additional *"Warning":* "Do not take this product for persistent cough such as occurs with smoking, asthma, emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a physician".

B. CATEGORIZATION OF DATA

1. *Category I conditions under which antitussive ingredients are generally recognized as safe and effective and are not misbranded.*

Category I—active ingredients

The Panel has classified the following antitussive active ingredients as general-

ly recognized as safe and effective and not misbranded:

Codeine preparations: Codeine, Codeine alkaloid, Codeine phosphate, Codeine sulfate
Dextromethorphan
Dextromethorphan hydrobromide
Diphenhydramine hydrochloride

a. *Codeine preparations (codeine, codeine alkaloid, codeine phosphate, codeine sulfate).* The Panel concludes that codeine and its salts are safe and effective for OTC use as antitussives as specified in the dosage section discussed below.

(1) *Safety.* Side effects such as drowsiness, light headedness, excitement, loss of appetite, nausea, vomiting, headache, abdominal discomfort and constipation with oral doses of 20 mg of codeine have not been significantly greater than with placebo (Ref. 1). The Panel has reviewed the literature and finds that respiratory depression may occur but is usually seen when codeine products are used as prescription medication with dose levels of 120 mg every 4 hours which results in the codeine having analgesic activity similar to that of 10 mg of morphine (Ref. 2). Such high doses of codeine would present a real hazard in certain cases of respiratory disease associated with a tendency towards carbon dioxide retention. By central depression of respiration, the exchange of oxygen and carbon dioxide would be impaired and there would be a tendency for the carbon dioxide to accumulate in the blood resulting in or aggravating respiratory acidosis with a dulling of the senses progressing to coma. As little as 60 mg of codeine in adults has produced measurable respiratory depression, judging from carbon dioxide response curves (Refs. 3 and 4). This has not been apparent with the doses approved for OTC use. In an infant, doses of 10 mg every 2 hours for 10 doses has led to deep coma (Ref. 5). Death has occurred from overdosage with codeine in the range of 875 to 1,750 mg but effects were complicated by the presence of other central nervous system depressants (Ref. 6).

The Panel believes the potential for abuse of codeine is negligible (Refs. 7, 8, and 9). It is further the opinion of the Panel that under usual conditions of therapeutic use, codeine has low dependency liability. Codeine may cause addiction, but requires consistently high daily dosage (Ref. 9). (See part II. paragraph G. above—Drug Misuse and Abuse.)

(2) *Effectiveness.* A paper by Eddy et al. (Ref. 10) summarized all the data in animals and indicates the varied techniques used and results obtained. Practically all animal studies have demonstrated the ability of codeine to suppress the cough reflex.

Studies of experimentally produced cough in man were also reviewed by Eddy et al. (Ref. 10). Cough-inducing agents used were citric acid aerosol, ammonia vapour, acetylcholine aerosol, peppermint water spray, and paraldehyde. The dose of codeine ranged from 5 mg to 120 mg with most investigators using 15 to 30 mg and they were able to demonstrate a cough suppressant effect in humans.

Eddy's review of 33 clinical trials by 16 investigators (Ref. 10) indicated that codeine in doses ranging between 10 to 60 mg was an effective cough suppressant in a wide variety of disease states associated with cough. Twenty-four of these studies employed objective cough-counting techniques. All had placebo controls, and many compared codeine with other drugs as well. While all of the objective studies employed patients with chronic cough (Refs. 11 through 16), two of the subjective studies employed patients with an acute cough due to an upper respiratory infection (Refs. 17 and 18).

The technique of employing citric acid aerosols to stimulate the cough reflex in healthy subjects (Ref. 19) has also been used to demonstrate the effectiveness of codeine as an antitussive in dose ranges of 15 to 30 mg.

There are no well-controlled studies on the antitussive activity of codeine in children, and hence, dosage recommendations in children have been based on the general experience of a Pediatric Panel, which reviewed these recommended dosages. (See part II. paragraph H. above—Pediatric Dosage.) Because the majority of clinical trials have been in chronic cough, the Panel has accepted the principle that the effectiveness of codeine in coughs due to upper respiratory infection may, in large measure, be extrapolated from the information on antitussive activity in chronic cough. This is further supported by an extensive clinical experience with the use of codeine over the past 50 years.

Because of abuse liability of codeine if available as a single ingredient in unlimited supply, the Panel concurs with the present Drug Enforcement Agency regulations, which limit the sale of codeine over-the-counter. These regulations limit the amount of codeine or its salts contained in an OTC product to 200 mg per 100 ml for liquid preparations or 200 mg per 100 gm for solid dosage forms (21 CFR 1308.15(b)(1)). These regulations further specify that codeine for OTC purchase must include one or more nonnarcotic active medicinal ingredients in sufficient proportion to confer medicinal qualities upon the product other than those possessed by codeine alone (21 CFR 1308.15(b)). In addition, these regulations limit OTC sale of such codeine containing products to quantities not exceeding 120 ml or 24 dosage units (21 CFR 1306.32(b)).

(3) *Dosage.* Adult oral dosage is 10 to 20 mg every 4 to 6 hours not to exceed 120 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 to 10 mg every 4 to 6 hours not to exceed 60 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 to 5 mg every 4 to 6 hours not to exceed 30 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive ingredients. (See part III. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling claims referrable to a central mechanism of action: (i) *Indications.* "Calms the cough control center and relieves coughing".

(ii) *Warnings.* (*a*) "May cause or aggravate constipation".

(*b*) "Do not give this product to children taking other drugs except under the advice and supervision of a physician".

(*c*) "Do not take this product if you have a chronic pulmonary disease or shortness of breath except under the advice and supervision of a physician".

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b. *Dextromethorphan, dextromethorphan hydrobromide.* The Panel concludes that dextromethorphan and dextromethorphan hydrobromide are safe and effective for OTC use as antitussives as specified in the dosage section discussed below.

(1) *Safety.* Dextromethorphan is the dextrorotatory isomer of the morphinan molecule which, unlike the levo isomer, has no analgesic or addictive properties (Ref. 1). With usual antitussive doses, no effect has been noted on respiration, the cardiovascular system, or the gastrointestinal tract. With very large doses such as occur in drug abuse or accidental poisoning, respiratory depression has been noted (Refs. 2 and 3). However, no fatalities have been reported, even with doses in excess of 100 times the normal adult dose. Abuse has been reported by Degkwitz (Ref. 4) with doses of 300 to 1,500 mg several times daily, resulting in intoxication with bizarre behavior but no physical dependence.

(2) *Effectiveness.* Dextromethorphan is an active antitussive comparable to codeine on a mg-for-mg basis for cough suppression. Studies involving many species of animals and many methods for inducing cough have demonstrated that effectiveness of dextromethorphan as an antitussive is comparable to codeine (Refs. 5 through 7). Two studies (Refs. 8 and 9) reported that dextromethorphan was less effective than codeine in equivalent doses. It has been demonstrated that dextromethorphan, like codeine, acts through central (brain) inhibition of incoming cough stimuli (Refs. 10 and 11).

There have been a large number of studies in man over the past 20 years. These have consisted of: Experimentally induced cough with controlled double-blind crossover designs (Refs. 12 through 15) in which all but one (Ref. 13) showed effective antitussive activity; controlled subjective studies in pathologic cough (Refs. 13, 16 through 18); controlled objective studies in pathologic cough (Refs. 19 and 20); and uncontrolled subjective studies in a variety of disease states resulting in cough (Refs. 21 and 22).

The wide range of safety and low order of toxicity in clinical trials has been documented by Ralph (Ref. 21). The lack of addiction liability has been confirmed recently by Mansky and Jasinski (Ref. 23).

The majority of these clinical studies demonstrate effective antitussive activity. Even though a few of the studies questioned the effectiveness of dextromethorphan, the Panel concluded that based on the evidence presented, dextromethorphan is generally recognized as effective, and because of its low order of toxicity it is probably the safest antitussive presently available.

(3) *Dosage.* Adult oral dosage is 10 to 20 mg every 4 hours or 30 mg every 6 to 8 hours not to exceed 120 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 to 10 mg every 4 hours or 15 mg every 6 to 8 hours not to exceed 60 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 to 5 mg every 4 hours or 7.5 mg every 6 to 8 hours not to exceed 30 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling claims referrable to a central mechanism of action and its nonnarcotic designation: (i) *Indications.* (*a*) "Calms the cough control center and relieves coughing".

(*b*) "Non-narcotic cough suppressant for the temporary control of coughs".

(*c*) "Calms cough impulses without narcotics".

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c. *Diphenhydramine hydrochloride.* The Panel concludes that diphenhydramine hydrochloride is safe and effective for OTC use as an antitussive as specified in the dosage section discussed below.

(1) *Safety.* Diphenhydramine was the first of the antihistamines to be developed in the U.S. and was first used in 1946, clinically, for the relief of a wide variety of allergic symptoms. Diphenhydramine had a low order of toxicity in laboratory animals combined with a high degree of antihistaminic action. The Panel reviewed a number of studies contained in the submissions (Refs. 1 and 2) and concluded that with the exception of sedation, adverse effects have been rare and the drug is safe. The Panel has also found the drug to be safe for use

as an antihistamine and this use is discussed elsewhere in this document. (See part VII. paragraph B.1.c. below—Diphenhydramine hydrochloride.)

Clinical experience indicates that about 50 percent of persons have drowsiness as a side effect when 50 mg is given (Ref. 3). A double-blind controlled study in 20 males showed no evidence of interference with tests for memory, rotary pursuit, or reaction time with diphenhydramine hydrochloride in doses of 12.5 and 25 mg (Ref. 4). In a double-blind controlled subjective study on 546 patients with acute upper respiratory infection, drowsiness was reported in 11 of 269 patients receiving 25 mg diphenhydramine 4 times daily over a 3 day period (Ref. 5). Two of 277 patients receiving placebo also reported drowsiness. In infants, high doses of diphenhydramine may cause excitement and convulsions (Ref. 1). The acute toxicity of diphenhydramine in a variety of animal species is similar to other antihistamines such as pyribenzamine (Ref. 6). In children, 20 to 30 tables or capsules containing 50 mg each may represent a lethal or near lethal dose (Ref. 3).

The Panel has recommended specific warnings (see below) because an atropine-like effect is described by patients which includes a drying sensation of the mouth and nose and difficulty with urination in patients with enlarged prostates.

The Panel is aware that recently there was some concern expressed about the potential for misuse and abuse of diphenhydramine. This concern was contained in the statement of the Commissioner of Food and Drugs, which was included in the preamble to the report of the OTC Advisory Panel on Sedatives, Tranquilizers and Sleep-Aid Drug Products and published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292). This Panel will not attempt to comment on the findings of the other Panel or on the societal impact or abuse potential of diphenhydramine when used as an OTC nighttime sleep-aid. However, after a review of all the available data, the Panel concluded that diphenhydramine, as well as the other antihistamines reviewed, have a very low abuse potential and that there is little if any evidence of tolerance or habituation. However, the Panel does recognize that doses of diphenhydramine higher than those recommended for OTC use are likely to result in some side effects but that these side effects are sufficient to discourage abuse or misuse. In addition, the two pharmacologic groups for which this Panel is recommending diphenhydramine for OTC use, i.e., as an antitussive and as an antihistamine, are not recognized as being abusable by the drug abusing subculture. It should also be noted that diphenhydramine is available without a prescription for use as an antihistamine in Canada, the United Kingdom, and many other industralized countries of the world. The Panel was unable to determine that significant abuse of this ingredient was a problem in any of these countries.

The Panel concludes that diphenhydramine hydrochloride is safe for OTC use as an antitussive in the dosage ranges described below.

(2) *Effectiveness.* A number of animal studies employing chemical and mechanical methods for inducing cough (Refs. 7 through 9), including stimulation of the superior laryngeal nerve, the nerve that supplies the larynx and upper airway (Ref. 10), have demonstrated a reduction in cough frequency, which ranges from 25 percent to 120 percent of that produced by codeine depending on the species of animal employed and the method for inducing cough. The exact mechanism of action of diphenhydramine is not precisely known. However, because of its ability to inhibit the cough reflex resulting from stimulation of the superior laryngeal nerve, the Panel believes a central site of activity of diphenhydramine is a reasonable mode of action. Furthermore, the animal studies are cited as evidence that cough inhibition is not due to a general depression of the central nervous system but to a specific action, similar to codeine, on the "cough center".

Studies in man have consisted of: Experimentally induced cough employing a controlled double-blind crossover design in which both the 25 and 50 mg dose of diphenhydramine hydrochloride produced significant cough suppression equivalent to 15 mg of codeine (Refs. 11 through 13); two double-blind controlled objective studies in chronic cough, which showed antitussive activity for both 25 and 50 mg diphenhydramine hydrochloride as compared with placebo (Refs. 14 and 15), and the most common adverse reaction was drowsiness; controlled subjective study in chronic cough (Ref. 16) demonstrating antitussive activity superior to placebo but less than codeine; two subjective studies in acute upper respiratory infections, one controlled and one uncontrolled (Refs. 5 and 17), yielding equivocal results; and two objective cough counting studies in chronic cough, which were uncontrolled and showed a decrease in cough with all treatments (Refs. 18 and 19).

While drowsiness did not appear to be a major problem in the single dose studies, it is quite conceivable that repetitive doses may cause profound drowsiness in susceptible individuals. Furthermore, the drying effect of the drug's antihistaminic action could hinder bronchial drainage in patients with productive cough by making the secretions thicker and more difficult to expectorate.

(3) *Dosage.* Adult oral dosage is 25 mg every 4 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 mg every 4 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III, paragraph B.1 below—Category I Labeling.) In addition, the Panel recommends the following specific labeling claims referable to a central mechanism of action and its nonnarcotic designation: (i) *Indications.* (*a*) "Calms the cough control center and relieves coughing".

(*b*) "Non-narcotic cough suppressant for the temporary control of coughs".

(*c*) "Calms cough impulses without narcotics".

(ii) *Warnings.* (a) "May cause marked drowsiness".

(*b*) "May cause excitability especially in children".

(*c*) "Do not take this product if you have glaucoma or have difficulty in urination due to enlargement of the prostate gland except under the advice and supervision of a physician".

(*d*) *"Caution.* Avoid driving a motor vehicle or operating heavy machinery".

(*e*) "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(iii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 6.25 mg every 4 hours not to exceed 37.5 mg in 24 hours.

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Category I Labeling

The Panel recommends the following Category I labeling for antitussive active ingredients to be generally recognized as safe and effective and not misbranded as well as the specific labeling discussed in the individual ingredient statements:

a. *Indications.* (1) "Cough suppressant which temporarily reduces the impulse to cough".

(2) "For the temporary relief of cough due to minor throat and bronchial irritation as may occur with the common cold (cold) or with inhaled irritants".

(3) "Temporarily quiets coughing by its antitussive action".

(4) "Temporarily helps you cough less".

(5) "Temporarily helps to quiet the cough reflex that causes coughing".

b. *Warnings.* (1) "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(2) "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a physician".

(3) *"Caution:* A persistent cough may be a sign of serious condition. If cough persist for more than 1 week, tends to recur or is accompanied by high fever, rash or persistent headache, consult a physician".

2. *Category II conditions under which antitussive ingredients are not generally recognized as safe and effective or are misbranded.* The use of antitussives under the following conditions is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel concludes that the following ingredients and labeling should be removed from the market until scientific testing supports their use.

Category II Active Ingredients

The Panel has classified the following antitussive active ingredients as not generally recognized as safe and effective or as misbranded:

Hydrocodone bitartrate (dihydrocodeinone)

Turpentine oil (spirits of turpentine) (oral)

a. *Hydrocodone bitartrate (dihydrocodeinone).* The Panel concludes that hydrocodone bitartrate (dihydrocodeinone) is safe for prescription use but that its addiction potential and other adverse reactions, including respiratory depression, are so serious that it is not appropriate for OTC use. The Panel concludes that the current prescription status of hydrocodone bitartrate under the Federal Controlled Substances Act is appropriate and that the ingredient should not be available as an OTC antitussive.

(1) *Safety.* Pharmacologically, hydrocodone is a more potent antitussive and analgesic than codeine and its adverse reactions, including addiction potential, are greater than codeine (Refs. 1 through 3). Depression of respiration has been noted in animals (Ref. 4) and man (Ref. 5). The addiction problem, which approaches that of the more potent narcotics such as morphine, has been reviewed by Rosenwald and Russell (Ref. 6). Because its potency as a narcotic falls between morphine and codeine, respiratory depression can be a real hazard with hydrocodone, especially in patients with chronic obstructive pulmonary disease.

(2) *Effectiveness.* Hydrocodone is an active antitussive with a potency approximately three times that of codeine on a weight basis.

A number of uncontrolled clinical trials (Refs. 7 through 10) suggest effective antitussive activity in chronic lung disease, including pulmonary tuberculosis lasting for 8 to 12 hours. A subsequent double-blind clinical trial (Ref. 11) and experimental cough-challenge study (Ref. 12) confirmed its antitussive activity.

(3) *Evaluation.* The Panel concludes that the activity of hydrocodone bitartrate in chronic and serious diseases make it a valuable drug for use under proper medical supervision and for that reason recommends that its availability continue to be restricted to prescription use only, under the Federal Controlled Substances Act.

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b. *Turpentine oil (spirits of turpentine) (oral).* The Panel concludes that oil of turpentine is not safe for OTC use when taken orally as an antitussive.

(1) *Safety.* Oil of turpentine is a volatile oil distilled from turpentine, an oleoresin obtained from the pine tree. It has a characteristic odor and taste. The substance has been administered orally, topically, and by inhalation.

In doses of 15 ml in children and 150 ml in adults fatal poisoning may occur (Ref. 1). Excessive oral doses produce marked irritation of the alimentary tract, especially of the stomach and of the pelvic organs. Toxic symptoms include vomiting, diarrhea, acute pain, renal irritation, bloody stools and hyperemia of all abdominal organs. Continued use may lead to cloudy swelling and fatty degeneration of the liver. Abnormal central nervous system symptoms may develop (Refs. 2 and 3).

Since no safe oral dose has been established for effective use as an antitussive, the Panel concludes that turpentine oil should not be available for oral OTC use as an antitussive. However, elsewhere in this document, the Panel concludes that the ingredient is safe when applied topically or used as an inhalant but that there are insufficient data to permit final classification of its effectiveness for inhalant or topical use as an antitussive. (See part III. paragraph B.3.1. below—Turpentine oil (spirits of turpentine) (topical/inhalant).)

(2) *Effectiveness.* Oil of turpentine is irritating and its chief suggested uses are based on this property (Refs. 1 and 4). There is no evidence to support its effectiveness as an antitussive when taken orally.

(3) *Evaluation.* The Panel is unable to determine a safe oral dose for turpentine oil for use as an antitussive. The Panel is of the opinion that the risk from oral administration outweighs whatever benefit might occur. Therefore, the Panel concludes that turpentine oil is not safe for oral use as an antitussive.

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Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety and/or effectiveness of the product is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel has previously discussed such labeling. (See part II. paragraph O. above—CCABA Product Labeling Claims Not Supported by Scientific Evidence.) However, labeling that is descriptive of the product such as its taste or appearance is acceptable.

Unacceptable claims for antitussives include any statement containing the term chest or lung congestion. The term "congestion", which may be interpreted by the target population to denote a discomfort of the chest, may result from a variety of causes, several of which may be of a most serious nature and require professional attention.

All claims that state or imply a therapeutic action or safety property peculiar to the preparation that cannot be demonstrated in controlled studies are not acceptable, e.g., "specially formulated", "improved", or "selected", "natural", "extra strength", "teamed components", "superior to ordinary", "modern", and "superior".

Statements alluding to greater potency, such as "extra strength" or "contains more antitussive per dose" are misleading because there are no acceptable controlled studies documenting that one preparation is more potent than another, particularly for Category I drugs. There is also no justification for claiming more antitussive per dose because there is no scientific merit from a therapeutic point of view between 15 mg of drug A and 30 mg of drug B if they are both effective. Therefore, any claim for "extra strength" or "higher dose level" may be misleading in that the product is no more effective and in fact may increase the potential for side effects. Under such circumstances the Panel feels that all such claims are misleading to the consumer.

Claims implying a physiological effect that either has no foundation or meaning will be meaningless to the public are unacceptable; such as, "gets to the roots of", "recommended by doctors", "travels through the blood stream", "works internally".

Claims for relief where time is indeterminate and not supported by scientific data are unacceptable; such as, "fast" and "prompt".

Statements such as "a dramatic advance", "the greatest advance in cough relief", "the modern way to stop coughs" etc., are vague generalizations, which imply a superiority of a product. These statements cannot be supported by scientific evidence, and since they are meaningless, can only have the effect of misleading the consumer.

The Panel concludes that such labeling should be removed from the market until scientific testing supports their use.

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel concludes adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed ingredients and conditions listed below. The Panel believes it reasonable to provide 4 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within 4 years, however, the ingredients and conditions listed in this category should no longer be marketed in over-the-counter products. Effectiveness as an antitussive must be demonstrated by controlled objective studies employing cough-counting techniques. Subjective data, alone, are unacceptable because of the marked variability in the subjective awareness of cough. Studies have shown (Refs. 1 and 2) that there is a poor correlation in the subjective appraisal of the effectiveness of the cough suppressant and the actual objective studies done by employing cough-counting techniques.

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Category III Active Ingredients

The Panel concludes that the available data are insufficient to permit final classification of the following claimed antitussive active ingredients:

Beechwood creosote
Camphor (topical/inhalant)
Caramiphen edisylate (caramiphen ethanedisulfonate)
Carbetapentane citrate
Cod liver oil
Elm bark
Ethylmorphine hydrochloride
Eucalyptol/eucalyptus oil (topical/inhalant)
Horehound (horehound fluidextract)
Menthol/peppermint oil (topical/inhalant)
Noscapine (noscapine hydrochloride)
Thymol (topical/inhalant)
Turpentine oil (spirits of turpentine) (topical/inhalant)

a. *Beechwood creosote.* The Panel concludes that beechwood creosote is safe in the dosage range used as an antitussive, but there are insufficient data to permit final classification of its effectiveness for OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that beechwood creosote in the usual doses contained in lozenges or cough mixtures for antitussive activity is safe.

Creosote is a distillate of wood tar and has a smokey color and a pungent taste. Dosages in excess of 4 gm 3 times daily produce giddiness, dimness of vision, circulatory collapse, convulsions and coma (Ref. 1). Because of the taste, it is normally given well-diluted (Ref. 2). Occasional adverse gastrointestinal side effects are mentioned in one report but are poorly documented (Ref. 3). Based on the available data and the presence of beechwood creosote on the market for many years, the Panel concludes that this ingredient is safe for OTC use.

(2) *Effectiveness.* There are no well-controlled objective studies documenting the effectiveness of beechwood creosote, alone, as an antitussive. Only one submission to the Panel (Ref. 4), reports a double-blind controlled study, for a combination product containing creosote, in 25 patients with chronic cough employing cough-counting techniques, which is said to show transient drug activity with statistical significance at 1 hour after drug administration. The statistical analysis and methodology is cumbersome and confusing. It is unclear whether a significant difference from the placebo was obtained. Because the dose of the product is unstated there is a lack of information regarding the smoking habits of the subjects in this study, and no evidence to indicate that the high speed, automatic electronic counter is accurate and reliable by comparing it with actual cough counts, serious questions are raised by the Panel about the acceptability of this study.

According to the standard compendia (Refs. 1 and 5), an average dose of beechwood creosote is 250 mg 3 or 4 times daily. In the two submissions to the panel listing of creosote, the dosages are 3.29 mg/lozenge and 33 mg/15 ml every 3 hours (Ref. 6). This 40 to 80 fold differ-

ence in dose (3.29 mg/lozenge, 8 doses/daily) appears illogical, and there is no evidence to indicate that creosote is effective in such low doses. The Panel concludes that further studies are needed to determine effectiveness.

(3) *Proposed dosage.* Adult oral dosage is 250 mg every 4 to 6 hours not to exceed 1500 mg in 24 hours. Children 6 to under 12 years oral dosage is 125 mg every 4 to 6 hours not to exceed 750 mg in 24 hours. Children 2 to under 6 years oral dosage is 62.5 mg every 4 to 6 hours not to exceed 375 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness as an antitussive will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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b. *Camphor (topical/inhalant).* The Panel concludes that camphor is safe in the dosage ranges used when applied topically or as an inhalant, but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that camphor (topical/inhalant) is safe in the dose ranges used as an antitussive.

Camphor is a local irritant producing skin redness when rubbed on the skin. However, when not vigorously applied, it may produce a feeling of coolness on the skin as does menthol. It acts similarly on the respiratory tract. Taken orally in small doses it produces a feeling of warmth and comfort in the stomach, but in larger doses it is irritating and can cause nausea and vomiting. Camphor also has a mild local anesthetic action, and its application to the skin may be followed by numbness. The systemic effects are primarily related to stimulation of the central nervous system. The ingestion of solid camphor by children can cause convulsions (Ref. 1). As little as 0.75 gm of camphor (equivalent to a teaspoonful of liniment of camphor or camphorated oil, which contain 20 percent camphor) has been fatal to a child. Commercially available ointments containing mixtures of volatile substances for use as decongestants or antitussives contain about 5 percent camphor. Since it is conceivable that ingestion of a sufficient amount of such a preparation could produce toxic effects in a young child, a suitable warning should be present on the label. The ingestion of 2 gm of camphor generally produces toxic effects in an adult, although up to 45 gm has been ingested with recovery (Ref. 2).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of camphor (topical/inhalant) as an antitussive. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

Studies involving objective measurement of antitussive activity of camphor primarily involve mixtures of volatile substances topically applied as ointments (Refs. 3 and 4), as steam inhalations (Refs. 5 through 7), and as lozenges (Refs. 8 and 9), evaluated against artificially induced cough in normal subjects by the citric acid aerosol method. In these studies, significant antitussive activity is demonstrated for a mixture of volatile substances containing camphor compared to placebo, but the contribution of the camphor component to this effect is not evident. In a crossover study involving 16 subjects, the effects of 5.3 percent camphor in a petrolatum ointment applied to the chests of subjects were compared to an ointment containing several volatile substances including 5.3 percent camphor and to a placebo (petrolatum) in suppressing a citric acid aerosol-induced cough. The combination ointment containing camphor induced a significant decrease in cough counts at all challenge times from ½ hour through 2 hours averaging about 20 percent decrease in cough counts at the ½- and 1-hour intervals, whereas the single ingredient camphor ointment yielded a significant decrease in cough counts just at the ½- and 1-hour intervals averaging about 10 percent reduction, and the petrolatum yielded no significant difference in cough counts compared with base line (Ref. 3).

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 5 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 7 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl or wash basin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 0.02 to 15 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations:

(i) For topical ointment use: Data to demonstrate effectiveness will require only one additional controlled cough-counting objective study in patients with coughs due to respiratory disease in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(iii) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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c. *Caramiphen edisylate (caramiphen ethanedisulfonate).* The Panel concludes that caramiphen edisylate is safe but there are insufficient data to permit final determination of its effectiveness for OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that caramiphen edisylate is safe in the dose ranges used as an antitussive. Acute and chronic toxicity studies in animals indicate a wide margin of safety, and caramiphen was judged to be considerably less toxic than codeine (Ref. 1). Instances of dizziness and drowsiness have been reported with dosage levels of 10 mg of caramiphen edisylate 3 times daily (Ref. 2). The incidence of these mild reactions increased when the dose was doubled, and one patient experienced a transient period of disorientation (Ref. 2). In a number of clinical trials, 12 of 172 patients reported adverse reactions, 4 of which were probably not drug related (Ref. 3). Although caramiphen pharmacologically is anticholinergic, with ½ to 1/10 the drying (antisecretory) effects of atropine, there have been no reports concerning its effect on bronchial secretions and no difficulty with retained secretions (Ref. 4).

At the average dose of 10 to 20 mg 3 to 4 times daily, few toxic reactions have been reported. Reported side effects have included slight nausea, dizziness, and occasional drowsiness, which appeared to be dose related. Until additional experience has accumulated, the labeling warning below concerning glaucoma and enlarged prostate, which may cause a block to the flow of urine, is deemed necessary in view of the drug's anticholinergic properties (Ref. 4).

(2) *Effectiveness.* There are no well-controlled objective, clinical studies documenting the effectiveness of caramiphen edisylate as an antitussive.

Studies in animals indicate that caramiphen is a centrally acting antitussive (Refs. 1 and 5). Cough suppression is due to an increase in the central threshold for cough. Almost all of the reports of studies are uncontrolled, subjective clinical trials (Refs. 6 and 7). Two controlled studies with induced cough showed 10 mg caramiphen to be singificantly superior to placebo but slightly less active than codeine 15 mg (Refs. 8 and 9). The only well-controlled crossover study was performed by Abelmann, Gaensler and Badger (Ref. 2), who concluded that caramiphen was superior to placebo but not as effective as codeine or dihydrocodeinone as a cough suppressant by subjective criteria, and that it decreased the amount of sputum in 61 percent of patients but without evidence of retention of secretions.

A controlled cough-counting study was recently reported in 25 patients with chronic cough (Ref. 10). The results of this study failed to show the efficacy of a single dose of 20 mg caramiphen as compared with placebo, but offered to show a significant antitussive effect after the fourth and fifth doses of the drug. Because of a lack of information regarding the smoking habits of the subjects in this study, and no evidence to indicate that the high speed, automatic electronic counter is accurate and reliable by comparing it with actual cough counts, serious questions about the acceptability of this study are raised.

(3) *Proposed dosage.* Adult oral dosage is 10 to 20 mg every 4 to 6 hours not to exceed 80 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 to 10 mg every 4 to 6 hours not to exceed 40 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 to 5 mg every 4 to 6 hours not to exceed 20 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific claims referrable to a central mechanism of action and its nonnarcotic designation: (i) *Indications.* (*a*) "Calms the cough control center and relieves coughing".

(*b*) "Non-narcotic cough suppressant for the temporary control of coughs".

(*c*) "Calms cough impulses without narcotics".

(ii) *Warnings.* (*a*) "Do not take this product if you have glaucoma or have difficulty in urination due to an enlarged prostate gland except under the advice and supervision of a physician".

(*b*) *"Caution:* Do not give this product to children taking other drugs except under the advice and supervision of a physician".

(5) *Evaluation.* Data to demonstrate effectiveness will be required from only one additional well-controlled cough-counting objective study in patients with cough due to respiratory disease in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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d. *Carbetapentane citrate.* The Panel concludes that carbetapentane citrate is safe but there are insufficient data to permit final determination of its effectiveness for OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that carbetapentane citrate is safe in the dose range used as an antitussive.

Studies in several animal species revealed a low order of toxicity, which was comparable to codeine phosphate (Ref. 1). Intravenous administration resulted in slight transient falls in blood pressure with no effect on respiration. In addition, carbetapentane possesses marked antispasmodic (relieves spasms) activity with weak anticholinergic (atropine-like) and local anesthetic properties. Adverse reactions in humans consisted for the most part of mild dryness of the mouth (Ref. 2). In this study, nine of 31 patients reported this side effect. An additional patient complained of severe nausea and loss of appetite and discontinued medication.

At an average dose of 25 mg 4 times daily, few side effects have been reported, and have consisted mostly of dryness of the mouth. On the whole, this atropine-like effect was mild and did not interfere with sputum production (Ref. 3), but the labeling warning (see below) concerning glaucoma and enlarged prostate is deemed necessary because of the anticholinergic properties of carbetapentane.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of carbetapentane citrate as an antitussive.

Animal studies employing a variety of methods for experimentally inducing cough as well as pathologic cough in dogs indicate that the onset of action and duration of cough suppression is equivalent to codeine (Refs. 1 and 4), but in a review of the literature (Ref. 5) there was considerable disagreement as to carbetapentane's relative antitussive potency as compared with codeine. Clinical studies were all subjective in type and only one had a placebo control (Ref. 6). At doses ranging between 7 and 25 mg 3 to 4 times daily, most investigators have reported "good" to "excellent" antitussive effect. Many of the clinical trials were of short duration in acute respiratory conditions and were uncontrolled (Refs. 3, and 7 through 9). The Council on Drugs of the American Medical Association has stated that, "available clinical evidence suggests that the effectiveness of the drug is limited to the acute (short duration) type of cough. Further and better controlled observations are

needed to establish its clinical usefulness" (Ref. 10). However, other investigators (Refs. 5, 11, and 12) have found carbetapentane to be effective in all types of cough. In one study, carbetapentane was not as effective as codeine for severe (intense and frequent) cough (Ref. 13). None of these clinical studies employed objective cough-counting techniques and few were adequately controlled.

(3) *Proposed dosage.* Adult oral dosage is 15 to 30 mg every 4 to 6 hours not to exceed 180 mg in 24 hours. Children 6 to under 12 years oral dosage is 7.5 to 15 mg every 4 to 6 hours not to exceed 90 mg in 24 hours. Children 2 to under 6 years oral dosage is 3.75 to 7.5 mg every 4 hours not to exceed 45 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific claims referable to a central mechanism of action and its nonnarcotic designation: (i) *Indications.* (*a*) "Calms the cough control center and relieves coughing".

(*b*) "Non-narcotic cough suppressant for the temporary control of coughs".

(*c*) "Calms cough impulses without narcotics".

(ii) *Warnings.* (*a*) "Do not take this product if you have glaucoma or have difficulty in urination due to an enlarged prostate gland except under the advice and supervision of a physician".

(*b*) "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(*c*) *"Caution:* Do not give this product to children taking other drugs except under the advice and supervision of a physician".

(5) *Evaluation:* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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e. *Cod liver oil.* The Panel concludes that cod liver oil is safe but there are insufficient data to determine its effectiveness for OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that cod liver oil is safe in the dose ranges used as an antitussive. Clinical experience over more than 100 years of use has demonstrated that cod liver oil is safe, and no significant evidence of toxicity has been reported when used in a wide variety of disease states as well as for vitamin supplementation. Rare instances of hypervitaminosis with resulting nausea, vomiting, and diarrhea have been reported with excessive doses (Ref. 1).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of cod liver oil as an antitussive. Except for a brief statement that cod liver oil is also given with benefit in "respiratory catarrhs" in subacute and chronic bronchitis, "catarrhal pneumonia," and frequent and persistent "colds" in children and the aged (Ref. 1), there is no actual reference to its value as a cough suppressant. In fact, all of the available references state that the value of cod liver oil in therapeutics lies in its high content of vitamins A and D (Refs. 2 and 3).

(3) *Proposed dosage.* The usual dosage is said to be 5 ml (1 teaspoon), which contains no less than 3,900 USP units of vitamin A and 386 USP units of vitamin D which provides the daily requirements for children and adults of both these vitamins (Refs. 3 and 4). The dosage of an emulsion containing 50 percent cod liver oil is 15 ml or 1 tablespoon (Ref. 2). However, all of these dosage forms refer to its use as a vitamin supplement.

The Panel is aware of one reference to a dosage of 2 teaspoons after each meal in convalescence from respiratory diseases. The duration of therapy is not stated (Ref. 2). The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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f. *Elm Bark.* The Panel concludes that elm bark (slippery elm, ulmus rubra) is safe but there are insufficient data to determine its effectiveness for OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that elm bark is safe in the dose ranges used as an antitussive. Clinical experience over a period of several hundred years has yielded no evidence of toxicity when used either as a lozenge, infusion for internal consumption, or as a poultice applied to the skin for antitussive action.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of elm bark as an antitussive. Elm bark was used by the Indians and early settlers of North America in the form of poultices and liquids for the treatment of fevers and colds with cough. It is referred to by Schopf in 1787 as "salve bark" (Ref. 1). The mucilaginous quality of these preparations is said to confer excellent protective demulcent properties, which were employed in the form of lozenges to relieve irritation of the pharynx (Ref. 2).

(3) *Proposed dosage.* The Panel is unable to determine a proposed dosage. Troches or lozenges of slippery elm are listed as containing 0.2 gm of elm per troche with the dosage being one troche, and the frequency of administration is given as "ad libitum" (Ref. 3). A warm infusion was prepared by stirring 1 oz of the powdered bark in a pint of hot water, which was then taken "ad libitum" (Ref. 2). The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends

that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See paragraph III. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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g. *Ethylmorphine hydrochloride.* The Panel concludes that ethylmorphine hydrochloride is safe but there are insufficient data to permit final determination of its effectiveness for OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that ethylmorphine hydrochloride is safe in the dose range used as an antitussive.

There are few well-documented studies in animals and man defining the incidence of adverse reactions. Ethylmorphine is the ethyl ether of morphine and its pharmacologic properties are similar to codeine, the methyl ether of morphine. Tolerance and physical dependence have been reported after prolonged use of ethylmorphine (Ref. 1). Other adverse reactions, such as constipation and respiratory depression, are similar to those of codeine. Topically, ethylmorphine is an irritant to mucous membranes and causes an inflammatory reaction with increased secretion of mucus (Ref. 2).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of ethylmorphine as an antitussive.

Animal studies employing induced cough showed ethylmorphine to have some antitussive activity (Refs. 3 and 4).

Since the early 1900's, ethylmorphine has been used clinically at approximately the same dosage level as codeine. Because of its failure to demonstrate any advantage over codeine, it never attained the popularity of codeine as an antitussive (Ref. 5), and hence there are few studies demonstrating its use as an antitussive. Only one paper reported that ethylmorphine in a dose of 15 to 22.5 mg was as effective as 30 to 60 mg of codeine in suppressing cough due to tuberculosis (Ref. 6). Unlike codeine, there are no objective clinical trials or well-controlled subjective studies in the literature.

Dosage range and pharmacologic activity, including adverse reactions and abuse potential, are similar to codeine. While ethylmorphine is regulated under the Federal Controlled Substances Act, it has not been tested at the Addiction Research Center, Lexington, KY because of its infrequent use (Ref. 5).

(3) *Proposed dosage.* Adult oral dosage is 15 mg every 4 to 6 hours not to exceed 90 mg in 24 hours. Children 6 to under 12 years oral dosage is 7.5 mg every 4 to 6 hours not to exceed 45 mg in 24 hours. Children 2 to under 6 years oral dosage is 3.75 mg every 4 to 6 hours not to exceed 22.5 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the labeling for Category I antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific claims referrable to its central mechanism of action: (i) *Indications.* "Calms the cough control center and relieves coughing".

(ii) *Warnings.* (*a*) "May cause or aggravate constipation".

(*b*) "Do not give this product to children taking other drugs except under the advice and supervision of a physician".

(*c*) "Do not take this product if you have a chronic pulmonary disease or shortness of breath except under the advice and supervision of a physician".

(5) *Evaluation:* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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h. *Eucalyptol/eucalyptus oil (topical/inhalant).* The Panel concludes that eucalyptol/eucalyptus oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that eucalyptol/eucalyptus oil (topical/inhalant) is safe in the dose ranges used as an antitussive.

Eucalyptus oil is about 70 percent active eucalyptol. Fatalities have followed doses of the oil as small as 3.5 ml, although recovery has occurred after doses of 20 and even 30 ml. Symptoms include epigastric burning with nausea and vomiting, vertigo, ataxia, muscle weakness and stupor (Refs. 1 and 2). A study of 223 subjects in which an ointment containing several volatile substances, including eucalyptus oil 1.3 percent, was applied for 48 hours to areas of intact skin under a patch and to abraded skin, revealed no instances of irritation, inflammation, wheal or hives following the period of exposure (Ref. 3). A study of 10 subjects who received application of an ointment containing several volatile substances, including eucalyptus oil 1.3 percent, to their trunks 3 times daily for 3 weeks, then 1 week off followed by another 1 week of treatment, revealed no local reactions during this subsequent challenge phase (Ref. 4). A study of infants and children with respiratory infection who received an ointment containing a mixture of volatile oils, including eucalyptus oil 1.3 percent, applied to the chest and neck demonstrated no adverse effect from inhaled vapors by that route of administration on the rate of clearing of laryngeal edema (Ref. 5).

Vapors are also produced by placing a liquid mixture of volatile substances, including eucalyptus oil 1.7 percent, in the water of a hot steam vaporizer and administered via inhalation. Exaggerated-use studies in adults and children, i.e., exposure for several hours to higher than recommended exposure concentrations of these vapors either due to sitting in closer proximity to the vaporizer or placing two to five times the recommended dose of the volatile substance in the vaporizer, were not associated with irritating or toxic effects (Refs. 6 and 7).

A series of studies assessing buccal safety and overt side effects from lozenges containing a mixture of volatile oils was conducted in over 300 subjects (Refs. 8 through 11). Lozenges containing up to 5.5 mg eucalyptus oil were dissolved in the mouth every hour for 8 hours on 2 successive days. Mild erythema of the buccal mucosa and tongue was observed but did not differ appreciably from the response to dissolving lozenge sugar base without volatile oils. The incidence of gastrointestinal symptoms did not differ from control either (Refs. 8 through 11).

An aerosolized dosage form of volatile substances including 1 percent eucalyptus oil has also been utilized for treatment of nasal congestion. In humans, such aerosol sprays have been generally safe when used as directed, but there have been reports of deaths from deliberate sniffing abuse, particularly when the subject inhales from a plastic bag into which the material has been sprayed (Ref. 12). Furthermore, one commercial preparation containing a particular solvent (1,1,1-trichloroethane) was recently

recalled from the market due to potential hazards of this substance (Ref. 13).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of ecualyptol/eucalyptus oil (topical/inhalant) as an antitussive. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

Eucalyptus oil is a component of a number of currently marketed OTC topically applied preparations utilized as antitussives, e.g., ointments, steam inhalation, and lozenges. In a crossover study involving 16 subjects, the effects of a 1.3 percent eucalyptus oil in petrolatum ointment applied to the chests of the subjects was compared to an ointment containing several volatile substances, including 1.3 percent eucalyptus oil, and to petrolatum in suppressing a citric acid aerosol induced cough. The combination ointment containing eucalyptus oil induced a significant decrease in cough counts at all challenge times from ½ hour through 2 hours averaging about 20 percent decrease at the ½ and 1 hour intervals, whereas the single ingredient eucalyptus oil ointment yielded a significant decrease in cough counts at the ½ hour through 1 and ½ hour intervals averaging about 15 to 18 percent reduction at these times, and the petrolatum yielded no significant decrease in cough counts compared with base line (Ref. 14). Similar results with a combination ointment containing 1.3 percent eucalyptus oil were obtained in two additional induced cough studies conducted by the same investigator (Refs. 14 and 15).

A single-blind crossover cough counting study of 27 patients exhibiting stabilized chronic cough, utilized twice daily chest application of either the ointment containing several volatile substances an ointment containing several volatile oils including 1.3 percent eucalyptus oil or a placebo (petrolatum base). Neither the ointment mixture of volatile substances nor the eucalyptus oil ointment induced a significant decrease in cough counts compared to placebo after the morning application, but a significant 20 percent cough count reduction compared to placebo was obtained following the afternoon dose of the ointment mixture. An average reduction in cough counts of about 10 percent compared to placebo was noted following the afternoon dose of eucalyptus oil ointment but this was not statistically significant (Ref. 16).

A liquid mixture of volatile substances was evaluated. The mixture was added to water of a hot steam vaporizer and administered via inhalation, and contains menthol 3.66 percent, camphor 7 percent, eucalyptus oil 1.7 percent and tincture of benzoin 5 percent. Three crossover studies compared the effects of this volatile substance containing liquid in steam (1 tablespoonful per quart of water) to steam alone in suppressing coughs artificially induced by the citric acid aerosol technique. In each case, both steam and medicated steam induced a statistically significant reduction in cough counts during the period of administration. In two of the studies the cough reduction with the medicated steam was statistically greater than with steam alone and persisted beyond the period of actual administration to the subjects (Refs. 17 through 19). In an objective cough counting study on patients with acute upper respiratory disease, the medicated steam showed significantly lower cough counts than the unmedicated steam for the 4 hours the patients were exposed to vaporization, and for 2 additional hours after vaporizer therapy was discontinued (Ref. 20). Subjective evaluation studies of adults and infants with cough associated with respiratory infection demonstrated statistically significant antitussive effectiveness of both the volatile substances in steam (1 tablespoon per quart) and of steam alone. In some of these studies the effect of the medicated steam was judged statistically superior to the steam alone (Refs. 21 and 22).

The variety of lozenge preparations containing a mixture of volatile substances that include eucalyptus oil have been studied for their ability to suppress citric acid aerosol induced cough in normal subjects. Since each of these lozenge preparations contain different concentrations of eucalyptus oil and other volatile substances, the study results will be individually summarized. The general study format involved a single blinded crossover design in which a group of cough standardized normal subjects were tested with each of two lozenge formulations, i.e., the active formulation and its vehicle control against cough artificially induced by the citric acid aerosol technique.

Two studies involving a total of 40 subjects used similar active formulations consisting of menthol 9.6 mg and eucalyptus oil 5.5 mg per lozenge. In these studies the active formulation produced significant cough reductions at the 10 to 40 minute challenge periods, reaching a peak of 25 to 35 percent reduction at the 10 and 20 minute intervals, whereas the control lozenge produced a significant reduction, 10 to 15 percent maximum, at only the 10 minute challenge (Refs. 23 and 24). In a study of 9 subjects receiving a two lozenge dose of menthol (1.0 mg/lozenges) and eucalyptol (7.6 mg/lozenge) elevated citric acid thresholds of 130 to 146 percent of control for 3 to 5 hours after dosing were obtained, although a placebo control lozenge was not utilized in this study for comparison (Ref. 25). Another study of 20 subjects utilizing a formulation of menthol 2.78 mg, eucalyptus oil 0.77 mg plus smaller amounts of camphor, thymol, and tolu balsam, produced significant cough reductions at the 10 through 40 minute challenge periods reaching a peak of 35 percent reduction at the 10 and 20 minute intervals whereas a control lozenge produced a significant reduction of 11 to 17 percent maximum at the 10 and 20 minute challenge periods only (Ref. 26). Similar results were obtained in 16 subjects using an active formulation containing menthol, eucalyptus oil, camphor, thymol and tolu balsum present in about one-half the amounts utilized in the preceding study (Ref. 27).

The effect of rinsing and gargling twice daily with an aqueous mixture of volatile substances on the incidence of colds and the severity of the symptoms associated with colds was evaluated in a long-term double-blind, placebo-controlled, subjective study in school children. The results of the study revealed milder nasal symptoms and cough symptoms in individuals using the medicated mouthwash as compared to the placebo. Although the medicated mouthwash contained 0.91 mg/ml eucalyptol, the results did not demonstrate the contribution of this component to the overall alleviation of symptoms (Ref. 28).

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 1.3 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 1.7 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl, or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 0.2 to 15 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

(iv) For use as a mouthwash 0.91/mg/ml solution: Gargle with ⅔ oz (20 ml) twice daily.

For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning*: "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning*: "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations:

(i) For topical ointment use: Data to demonstrate effectiveness will be required from only one additional controlled cough-counting objective study in patients with coughs due to respiratory disease in accordance with the guidelines set forth below for testing antitussive drugs.(See part III. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(iii) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(v) For use as a mouthwash: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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(28) OTC Volume 040278.

i. *Horehound (horehound fluidextract)*. The Panel concludes that horehound (marrubium) is safe but there are no data to evaluate its effectiveness for OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that horehound is safe in the dose ranges used as an antitussive. Horehound has been used for many centuries in the folk medicine of Europe in the form of a sweetened tea or bitter flavoring agent in decoctions and candies (Ref. 1). No adverse reactions have been cited and on the basis of long clinical experience, the Panel concludes that it is safe at the dose ranges employed for OTC use.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of horehound as an antitussive. There is no information available as to the effectiveness of horehound. It is stated that it was formerly used as an expectorant in various types of bronchitis but "has been abandoned by physicians" (Ref. 2). Another text (Ref. 1) states that it was dropped from the "Primary List" of drugs in 1910.

(3) *Proposed dosage.* The Panel is unable to determine a proposed dosage.

One marketed product for children contains the following dosage range: Children over 5 years oral dosage is 44 mg. Children 2 to 5 years oral dosage is 22 mg (Ref. 3). The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required according to the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.) However, the Panel notes that if claims for antitussive activity were withdrawn, this preparation could be considered a pharmaceutical necessity or flavoring agent.

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j. *Menthol/peppermint Oil (topical/inhalant)*. The Panel concludes that menthol/peppermint oil is safe in the dosage ranges used when applied topically as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that menthol/peppermint oil (topical/inhalant) is safe in the dosage ranges used as an antitussive.

Menthol is the chief constituent of peppermint oil comprising not less than 50 percent. It may be obtained by distillation of the oil or by synthesis (Ref. 1). Toxic effects with an excess ingestion of peppermint oil or mentholated products can include abdominal pain, nausea, vomiting, and symptoms of central nervous system depression such as dizziness, staggering gait, slowed respiration, flushed face, sleepiness, and coma (Refs. 2 and 3). The fatal oral dose of menthol itself in man is about 2 gm (Ref. 4). Topically applied menthol produces a cooling sensation presumably due to stimulation of the cold sensory receptors, whereas higher concentrations have irritant properties. In one study, a 20 percent solution of menthol in oil rubbed on to the skin induced an intense and lasting cooling sensation followed by numbness with slight burning and skin redness. A 0.5 percent solution applied to the nasal or oral mucosa was subjectively irritating, whereas a 0.2 percent solution was judged nonirritating (Ref. 5). A study of 223 subjects in which an ointment containing several volatile substances including menthol 2.8 percent was applied for 48 hours to areas of intact skin under a patch and to abraded skin revealed no instances of inflammation, wheal, hives, or primary irritation following the period of exposure (Ref. 6). Repeated topical application of mentholated products has been reported to give rise to hypersensitivity reactions, including contact der-

matitus (Ref. 4). A study of ten subjects who received an application of an ointment containing several volatile substances including menthol 2.8 percent to their trunks 3 times daily for 3 weeks, then 1 week off, followed by another week of treatment, revealed no local reactions during this subsequent challenge phase (Ref. 7). The incidence of hypersensitivity to menthol appears to increase with increased duration of use. For example, one survey revealed an incidence of less than 1 percent menthol hypersensitivity in 542 patients using a mentholated ointment for less than 10 years, whereas an incidence of 3.4 percent hypersensitivity was seen in 414 patients using this type of a preparation for longer than 10 years (Ref. 8).

In infants and small children under 2 years, intranasal use of ointments or drops containing high percentages of menthol may cause spasm of the glottis. A case of dangerous asphyxiation has been reported in a 3-week-old infant following intranasal application (Ref. 9). For this reason a warning against the topical application of menthol-containing products directly to the nostrils of infants has been recommended (Refs. 4 and 9). A study of infants and children with respiratory infection was made. They received an ointment containing a mixture of volatile oils including 2.8 percent menthol applied to the chest and neck; the study demonstrated no adverse effect from the inhaled vapors by that route of administration on the rate of clearing of laryngeal inflammation. In this study 35 children, 23 under 2 years of age, with respiratory infection received only standard forms of therapy, e.g., antibiotics and fluids, while 37 children, 30 under 2 years of age, received standard therapy plus the mentholated ointment to the chest and neck. Laryngoscopic examination revealed comparable rates of clearing of laryngeal inflammation (Ref. 10).

A liquid mixture of volatile substances including 3.66 percent menthol is placed in the water of a hot steam vaporizer and administered via inhalation. A number of studies involving nearly 900 subjects in which this mixture was administered at recommended doses was not associated with significant complaints of subjectively perceived adverse effects (Refs. 11 through 23). Exaggerated-use studies in adults and children, i.e., exposure for several hours to higher than recommended exposure concentrations, either due to sitting in closer proximity to the vaporizer or placing 2 to 5 times the recommended dose of the volatile substance in the vaporizer was not associated with irritating or toxic effects (Refs. 24 and 25).

In two studies, 40 healthy subjects who were each asked to dissolve two candy-base lozenges, each lozenge containing 1.36 mg of menthol together with other volatile oils, every 20 minutes for 2 hours exhibited no adverse effects with the exception of one report of nausea and vomiting. This was attributed to a dislike for the wild cherry flavor of the lozenge (Refs. 26 and 27). In a group of 70 healthy subjects, 50 adults and 20 children ages 8 to 12, half dissolved a menthol-eucalyptus lozenge containing 9.62 mg menthol and 5.55 mg eucalyptus oil every 4 to 8 hours on 2 successive days, the other half dissolved the cough drop base without the aromatics. In this intensive dosage schedule, a slightly larger number of subjects demonstrated mild irritation of the oral mucosa on days 1 and 2, but there were no differences between the two groups in the severity of irritation or residual findings after day 2. No systemic complaints were reported (Ref. 28). A similar study using a lozenge formulation containing menthol 8.14 mg and eucalyptus oil 4.625 mg versus a lozenge base without volatile substances produced comparable results (Ref. 29).

An aerosolized dosage form of volatile substances including 1 percent menthol has also been utilized for treatment of nasal congestion and cough symptoms. Rats exposed to acute overdoses of the spray in a confined chamber for 6 hours revealed no untoward behaviorial responses or airway tissues abnormality upon autopsy examination (Ref. 30). A group of four monkeys were exposed to 200 gm per day of the aerosol, i.e., 2 gm of menthol total dose in divided doses over an 8 hour period for 14 consecutive days in a confined chamber. Eye irritation was the only pharmacotoxic sign observed during the study (Ref. 31). In humans, such aerosol sprays have been generally safe when used as directed, but there have been reports of deaths from deliberate sniffing abuse, particularly when the subject inhales from a plastic bag into which the material has been sprayed (Ref. 32). Furthermore, one commercial preparation containing a particular solvent, 1,1,1-trichloroethane, was recently recalled from the market due to potential hazards of this substance (Ref. 33).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of menthol/peppermint oil (topical/inhalant) as an antitussive. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

The local anesthetic effect of menthol vapor has been the justification for including menthol in topically administered ointments and lozenges for alleviation of cough. In a crossover study involving 16 subjects, the effects of a 2.8 percent mentholated petrolatum ointment applied to the chest of the subjects was compared to an ointment containing several volatile substances including 2.8 percent menthol, and to petrolatum in suppressing a citric acid aerosol induced cough. A combination ointment containing menthol induced a significant decrease in cough counts at all challenge times from ½ hour through 2 hours, averaging about 20 percent decrease at the ½ and 1 hour intervals, whereas the single ingredient menthol ointment yielded a significant decrease in cough counts just at the ½ and 1 hour intervals, averaging about 10 percent reduction. The petrolatum yielded no significant decrease in cough counts compared with base line (Ref. 34). Similar results with the combination ointment containing 2.8 percent menthol were obtained in two additional induced-cough studies conducted by the same investigator (Refs. 34 and 35).

A single-blind crossover cough-counting study of 27 patients exhibiting stabilized chronic cough, utilized twice daily chest applications of either the ointment containing several volatile substances including 2.8 percent menthol, an ointment containing 1.3 percent eucalyptus oil, or petrolatum base. Neither the ointment mixture nor the eucalyptus oil ointment induced a significant decrease in cough counts compared to placebo after the morning application, but a significant 20 percent cough-count reduction compared to placebo was obtained following the afternoon dose of the ointment mixture. An average reduction in cough counts of about 10 percent compared to placebo was noted following the afternoon dose of eucalyptus oil ointment, but this was not statistically significant (Ref. 36).

A liquid mixture of volatile substances added to the water of a hot steam vaporizer and administered via inhalation contained menthol 3.66 percent, camphor 7 percent, eucalyptus oil 1.7 percent, and tincture of benzoin 5 percent. Three crossover studies compared the effects of this volatile substance containing liquid in steam, 1 tablespoonful per quart of water, to steam alone in suppressing coughs artificially induced by the citric acid aerosol technique. In each case, both steam and medicated steam induced a statistically significant reduction in cough counts during the period of administration. In two of the studies the cough reduction with the medicated steam was statistically greater than with steam alone and persisted beyond the period of actual administration to the subject (Refs. 37, 38, and 39). In an objective cough-counting study on patients with acute upper respiratory disease, the medicated steam showed significantly lower cough counts than does unmedicated steam for the 4 hours the patients were exposed to vaporization and for 2 additional hours after vaporizer therapy was discontinued (Ref. 40). Subjective evaluation studies of adults and infants having cough associated with respiratory infection demonstrated statistically significant antitussive effectiveness of the volatile substances in steam, 1 tablespoon per quart of water, and of steam alone. In some of these studies the effect of the medicated steam was judged statistically superior to the steam alone (Refs. 41 and 42).

The variety of lozenge preparations containing a mixture of volatile substances including menthol have been studied for their ability to suppress citric acid aerosol induced cough in normal subjects. Since each of these lozenge preparations contain different concentrations of menthol and other volatile substances, the results of the study will be individually summarized. The general study format involved an unblinded crossover design in which a group of

cough-standardized normal subjects were tested with each of two lozenge formulations, i.e., the active formulation and its vehicle control, against cough artificially induced by the citric acid aerosol technique. Two studies involved lozenges in which menthol was the principal active ingredient and consequently represent an indication of the effectiveness of this mode of administering menthol to suppress cough. One of the studies involving 16 subjects used a lozenge containing menthol 2.64 mg and peppermint oil 2.29 mg plus benzyl alcohol 5.76 mg. The active formulation produced significant cough reductions at the 10 to 40 minute challenge periods, reaching a peak of 30 to 35 percent at the 10 and 20 minute intervals, whereas the control lozenge produced a significant reduction of 15 to 20 percent at the 10 and 20 minute intervals only (Ref. 43). The other study of 10 subjects, utilizing a lozenge containing menthol 1.13 mg plus citric acid flavoring, produced greater cough reduction than the control lozenge at the 10 through 30 minute challenge periods, although both the active and control lozenges in this study produced cough reductions at these time intervals (Ref. 44).

Two studies involving a total of 40 subjects used similar active formulations consisting of menthol 9.6 mg and eucalyptus oil 5.5 mg per lozenge. In these studies the active formulation produced significant cough reductions at the 10 to 40 minute challenge periods, reaching a peak of 25 to 35 percent reduction at the 10 and 20 minute intervals, whereas the control lozenge produced a significant reduction of 10 to 15 percent maximum at only the 10 minute challenge (Refs. 45 and 46). In a study of nine subjects receiving lozenge doses of menthol 1.5 mg and eucalyptol 0.35 mg, elevated citric acid thresholds of 130 to 146 percent of control for 3 to 5 hours after dosing were obtained, although a placebo control lozenge was not utilized in this study for comparison (Ref. 47). Another study of 20 subjects utilizing a formulation of menthol 2.78 mg, eucalyptus oil 0.77 mg, plus smaller amounts of camphor, thymol, and tolu balsam, produced significant cough reductions at the 10 through 40 minute challenge periods, reaching a peak of 35 percent reduction at the 10 and 20 minute intervals, whereas a control lozenge produced a significant reduction of 11 to 17 percent maximum at the 10 and 20 minute challenge periods only (Ref. 48). Similar results were obtained in 16 subjects using an active formulation containing menthol, eucalyptus oil, camphor, thymol and tolu balsam present in about ½ the amounts utilized in the preceding study (Ref. 49).

The effect of rinsing and gargling twice daily with an aqueous mixture of volatile substances on the incidence of colds and the severity of the symptoms associated with colds was evaluated in a long-term, double-blind, placebo-controlled, subjective study in school children. The results of the study revealed milder nasal symptoms and cough symptoms in individuals using the medicated mouthwash as compared to the placebo. Although the medicated mouthwash contained 0.42 mg/ml menthol, the results did not demonstrate the contribution of this component to the overall alleviation of symptoms (Ref. 50).

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 2.8 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 3.66 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl, or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 1.0 to 15 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

(iv) For use as a mouthwash 0.42 mg/ml solution: Gargle with ⅔ oz (20 ml) twice daily.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required from only one additional controlled cough-counting objective study in patients with coughs due to respiratory disease in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(iii) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(iv) For use as a mouthwash: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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k. *Noscapine (noscapine hydrochloride).* The Panel concludes that noscapine is safe but there are insufficient data to determine its effectiveness for OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that noscapine is safe in the dosage ranges used as an antitussive. Noscapine belongs to the isoquinoline alkaloids of opium and, like papaverine, has a weak spasmolytic (relieves spasm) effect on smooth muscle but little or no effect on the heart or gastrointestinal tract (Ref. 1). There is no evidence that it causes addiction, and it is not subject to the Federal Controlled Substances Act. A large margin of safety in both animals and man has been reported (Refs. 2 and 3). Nausea, drowsiness, and lightheadedness have been reported in a few instances, but this was similar to the incidence in placebo reactors (Ref. 4). Bellville et al. (Ref. 5) found no depression of respiration with doses as high as 90 mg.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of noscapine as an antitussive. Effectiveness has not been established by objective, controlled clinical trials.

For the most part, the animal studies employing a variety of methodologies for inducing cough by mechanical and chemical means have shown noscapine to have an antitussive effect equivalent to codeine (Refs. 6, 7, and 8). Controlled studies in man using experimentally induced cough have been conflicting (Refs. 4, 9, and 10). Most of the clinical trials reported have been poorly controlled subjective studies. The majority of these studies indicate that noscapine is equal to codeine in clinical effectiveness (Refs. 3 and 11 through 15).

Unlike the narcotic antitussives, respiratory depression and constipation have not been reported for noscapine. Doses as high as 90 mg have been given with no significant increase in toxicity (Ref. 16).

(3) *Proposed dosage.* Adult oral dosage is 15 to 30 mg every 4 to 6 hours not to exceed a total of 180 mg in 24 hours. Children 6 to under 12 years oral dosage is 7.5 to 15 mg every 4 to 6 hours not to exceed 90 mg in 24 hours. Children 2 to under 6 years oral dosage is 3.75 to 7.5 mg every 4 to 6 hours not to exceed 45 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific claims referable to its central mechanism of action and its nonnarcotic designation:

(i) *Indications.* (*a*) "Calms the cough control center and relieves coughing".

(*b*) "Non-narcotic cough suppressant for the temporary control of coughs".

(*c*) "Calms cough impulses without narcotics".

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.) The Panel recommends that one experimentally induced cough study and one controlled study in patients with cough due to respiratory illness employing objective cough-counting techniques be performed in order to establish effectiveness as an antitussive.

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1. *Thymol (topical/inhalant).* The Panel concludes that thymol is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that thymol (topical/inhalant) is safe in the dosage ranges used as an antitussive.

Thymol is an alkyl derivative of phenol and has bactericidal, fungicidal and anthelmintic properties (Ref. 1). When hydrogenated, thymol is converted to the closely related drug, menthol (Ref. 2). The LD_{50} of thymol in mice is 1800 mg/kg orally (Ref. 3). No data were found bearing on the drug's toxicity in man. In view of thymol's relative inactivity compared to menthol, of which 50 to 120 gm "would have to be absorbed to cause poisoning" (Ref. 4), thymol is presumably relatively nontoxic.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of thymol (topical/inhalant) as an antitussive. Experiments in anesthetized rabbits have indicated that thymol administered by steam inhalation augmented the concentration of soluble mucous in the respiratory tract fluid (Ref. 2). The dose administered was unknown but the concentration in the vaporizer was in excess of 81 mg/kg. The volume of secretions did not change. Much lower concentrations of menthol were effective (1 mg/kg). In man no data on effectiveness of thymol alone were found although a mixture containing thymol, menthol, eucalyptol and propylene glycol appeared to suppress citric acid induced cough (Ref. 5) and to reduce resistance in the nasal and bronchial airways (Ref. 6).

Studies involving the objective measurement of the antitussive activity of thymol were done with mixtures of volatile substances, topically applied as ointments (Refs. 7, 8 and 9), and in steam inhalations (Refs. 10 and 11). Although significant antitussive activity as compared to placebo was demonstrated, it was not evident whether the thymol component contributed to this effect.

The effect of rinsing and gargling twice daily with an aqueous mixture of volatile substances on the incidence of colds and the severity of the symptoms associated with colds was evaluated in a long-term, double-blind, placebo-controlled, subjective study in school children. The results of the study revealed milder cough symptoms in individuals using the medicated mouthwash as compared to placebo. Although the medicated mouthwash contained 0.63 mg/ml thymol the results did not demonstrate the contribution of this component to the overall alleviation of symptoms (Ref. 12).

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 0.1 percent preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For inhalation use as a 0.13 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For inhalation use as a 0.1 percent room spray: Spray room for 15 to 20 seconds in the vicinity of the patient. May be repeated at ½ to 1 hour intervals as needed.

(iv) For topical use as a lozenge 0.2 to 15 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

(v) For use as a mouthwash 0.63 mg/ml solution: Gargle with ⅔ oz (20 ml) twice daily.

For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations: (i) For topical use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(ii) For inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(iii) For inhalation use as a room spray: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(iv) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(v) For use as a mouthwash: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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m. *Turpentine oil (spirits of turpentine) (topical/inhalant).* The Panel concludes that turpentine oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that turpentine oil is safe when applied topically or used as an inhalant in the dosage ranges used as an antitussive. The Panel concludes that oil of turpentine is safe when applied externally or vaporized in boiling water as a steam inhalant. However, the Panel has determined elsewhere in this document that it is not safe for OTC use when used orally as an antitussive. (See part III. paragraph B.2.b. above—Turpentine oil (spirits of turpentine) (oral).)

Oil of turpentine is a volatile oil consisting of a mixture of pinenes derived from the oleoresin obtained from Pinus palustrus. Nelson et al. (Ref. 1) found exposure to a vapor of 420 to 560 mcg/l acceptable to most of their human subjects. The threshold for industrial exposure for 8 hours has been set at 560 mcg/l. The maximum concentration obtainable with a currently marketed OTC preparation is 36 mcg/l (Refs. 2 and 3). No histological evidence of pulmonary lesions were seen in mice and rats exposed to lethal concentrations of turpentine vapors (Ref. 4). Inhalation of 300 mcg/l of turpentine vapor by mice for 15 minutes did not influence the electrocardiogram, respiratory minute volume, pulmonary airway, resistance, or compliance (Ref. 5). One study in mice using a mixture of volatile oils, one of which was turpentine, showed a decrease in pulmonary antibacterial activity (Ref. 6). Two other studies showed no change when the mixture was used (Refs. 7 and 8).

In several studies in children and infants suffering from minor breathing discomforts associated with the "common cold" no side effects that were drug related were observed when a medicated steam was administered (Refs. 9 through 13). Turpentine has been widely used as a part of a mixture of volatile oils for many years with approximately two complaints per million packages purchased (Ref. 14).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of turpentine oil (topical/inhalant) as an antitussive. Its effectiveness is uncertain due to a lack of properly controlled studies of the substance by itself.

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 4.0 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapor rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 5.5 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl, or washbasin; or 2 teaspoonful's of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations:

(i) For topical ointment use: Data to demonstrate effectiveness will be required from only one additional well-controlled cough-counting objective study in patients with coughs due to respiratory disease in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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Category III Labeling

The Panel concludes that the available data are insufficient to permit final classification of the labeling claims identified below for antitussives. The Panel concludes that certain words used in the context of claims for antitussives are statements which have no scientific meaning and therefore are misleading to the consumer. Additional data are required to support the following antitussive claims:

a. The term "soothing" in labeling such as "Calms coughing by soothing the irritated throat".

b. The term "throat soothing" in labeling such as "Throat soothing and recommended for coughs due to colds and dry, husky or tickling throats".

c. The term "smooth coating" in labeling such as "Produces a smooth coating that gives quick comfort to irritated throats and helps relieve coughs".

d. The terms "demulcent action" and "soothes" in labeling such as "Demulcent action which gently soothes cough-irritated throat membranes".

e. Statements referring to "duration of action" unless there is acceptable documentation to verify this.

f. Terms relating to sleep such as "Quiets annoying cough and lets you sleep". An antitussive is capable of quieting annoying cough, but has not been demonstrated to be directly related to sleep.

g. The term "soothing" has not been scientifically demonstrated to have an antitussive effect. In fact, none of the antitussive ingredients reviewed by the Panel have any "soothing" properties since the Panel cannot determine what such a property would be. The same is true for the term "smooth". Again, the Panel is unaware of how the ingredients act to smooth an irritated throat or sooth membranes by a "demulcent" action.

C. DATA REQUIRED FOR EVALUATION

The Panel has agreed that the protocols recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. *Principles in the design of an experimental protocol for testing antitussive drugs.* a. *General principles.* The effectiveness of an antitussive agent is dependent on its ability to relieve the coughing of patients with a variety of disease conditions associated with cough. Relief of coughing may occur with a reduction in the frequency or number of coughs, or with a decrease in the intensity of the coughing, or both. Because coughing is such a common symptom occurring in health as well as disease, adaptation readily occurs to the extent that many patients are unaware of the extent of their coughing, and hence any subjective evaluation is apt to be highly variable and with an unacceptable margin for error. Objective studies employing the actual recording of the cough are re-

quired to document a decrease in cough frequency and/or intensity.

b. *Selection of patients.* The study design will depend on whether the patients in the study have chronic lung disease or acute self-limiting illnesses. For a cough study in patients with chronic lung disease, a crossover design could be used in a small group of 10 to 20 patients whose underlying chronic pulmonary disease is relatively stable so that daily fluctuations in the recorded cough counts performed prior to drug administration are minimized. The smoking habit of the patients must be carefully documented and maintained at the same level throughout the clinical trials. No smoking would be permitted during the actual recording sessions. For a cough study in patients with acute upper respiratory infection, a larger number of patients, averaging between 50 and 100, would have to be studied because of the marked variation in cough from day to day and hour to hour in upper respiratory infection. The patients would have to be assigned in a randomized design to either the placebo or drug groups. The sensitivity of this type of study could be improved by matching the groups for age, sex, severity of cough, and smoking habit.

c. *Methods of study.* To establish effectiveness of a drug as an antitussive, objective controlled studies employing cough-counting techniques are recommended. Two types of investigation are acceptable to the Panel. These are:

(1) A study may be done in a small group of healthy volunteers, approximately 10 to 20 in number, who are preferably nonsmokers. If smokers are included, their smoking habits must be well documented and remain at the same level during the entire course of the study. Any departure from smoking habits must be documented and made part of the evaluation of data. The data obtained in such a study including smokers and nonsmokers should be evaluated separately before combined. A challenge technique employing an irritant aerosol such as citric acid is used to assess effectiveness, dose, and time responses against the experimentally induced cough. This is performed under controlled laboratory conditions with a double-blind or suitably blinded, crossover design in suitably trained individuals.

(2) A double-blind, controlled study may be done in patients with cough due to respiratory disease. The dose and formulation of the drug to be tested would be as recommended for OTC use. Coughs are recorded and counted for stated periods before and after giving the drug or placebo so that adequate comparisons can be made concerning the onset and duration of antitussive activity following a single dose, as well as the effect of multiple doses. As a model for OTC drugs, however, the requirement for long periods of testing would be unnecessary since effective relief should be obtained fairly rapidly and, in most instances, after 1 or, at most, 2 days.

d. *Interpretation of data.* Evidence of drug effectiveness is required from a minimum of two positive studies based on the results of two different investigators or laboratories. All of the required studies in man should employ objective cough-counting techniques for recording the cough reflex. In the reevaluation of those drugs for which there was insufficient evidence of antitussive effectiveness and for the assessment of drugs that have not been submitted for review by the Panel, the two required studies should consist of either one challenge study with experimentally induced cough plus a study with cough in respiratory disease, or, alternatively, two studies by different investigators in patients with respiratory disease. A significant reduction in cough when compared with placebo by acceptable statistical analysis of the data will permit reclassification of such drugs into Category I.

All data submitted to the Food and Drug Administration must present both favorable and unfavorable results.

c. *Evaluation of safety.* Tests for safety should involve the usual tests for toxicity relevant to the known possible adverse effects of the drugs under testing. Tests should be done in the form of dose-response curves up to maximum therapeutic effectiveness.

IV. EXPECTORANTS

A. GENERAL DISCUSSION

Expectorants are agents that are used to promote or facilitate the evacuation of secretions from the bronchial airways to provide for the temporary relief of coughs due to minor throat and bronchial irritation as may occur with upper respiratory infection. This may be accomplished by reducing the thickness of these secretions or by augmenting the formation of a more fluid secretion. The secretions (sputum or phlegm) expectorated consists in part of respiratory tract fluids (RTF) together with a varying mixture of saliva and postnasal secretions.

In general, the mechanisms of action of the expectorants have been shown to be due to one or more of the following: The stimulation of reflexes from the stomach (the major action of certain drugs that are irritants to the gastrointestinal tract and act through their nauseant effect which increases the output from the secretory glands of the gastrointestinal as well as the respiratory tracts); stimulation of vagal nerve endings in the glands of the bronchial tubes; direct effect on the secretory cells lining the airway when administered by inhalation or if excreted by the respiratory tract; and stimulation of centers in the brain such as the vomiting center.

By facilitating the evacuation of secretions from the bronchial airway, local irritants are removed. In addition, by increasing the amount of mucous that covers and protects the lining of the throat and the bronchial airway, it is claimed that a "soothing" or demulcent" action is exerted which relieves irritated membranes in the respiratory passages. While these effects may indirectly serve to diminish the tendency to cough, the mechanism of this indirect action is quite different from that of an antitussive which is specifically designed to inhibit or suppress cough. Any claim relating to the amelioration of cough must be supported by the type of studies suggested above for evaluation of antitussives. (See part III. paragraph C. above—Data Required for Evaluation.) Expectorants would be expected to have their major usefulness in the irritative nonproductive cough as well as those coughs productive of scanty amounts of thick, sticky secretions.

As a group, the expectorant drugs have been widely used for many decades in the form of liquid preparations. By and large, in the dosages used for OTC administration, these drugs have had a good safety record. The few exceptions, where hypersensitivity reactions or cumulative toxicity represents a distinct hazard, have been discussed under the individual sections. While the expectorants have been traditionally used for their effect on aiding in the expectoration of phlegm (sputum) and thus relieving certain aspects of difficulty in breathing, there is little or no evidence to document this. In summary, the Panel concludes that while many of the expectorants on the market with long usage are generally safe, most lack evidence of efficacy and furthermore, all expectorants must be clearly identified on the labels of drug products as having a primary effect on respiratory sputum and not primarily as an antitussive.

B. CATEGORIZATION OF DATA

1. *Category I conditions under which expectorant ingredients are generally recognized as safe and effective and are not misbranded.*

Category I Active Ingredient

The panel was unable to classify a claimed expectorant active ingredient as generally recognized as safe and effective and not misbranded.

Category I Labeling

The Panel recommends the following Category I labeling for expectorant active ingredients to be generally recognized as safe and effective and not misbranded:

a. *Indications.* (1) "Helps loosen phlegm (sputum)".

(2) "Helps rid the passageways of bothersome mucus".

(3) "Expectorant action to help loosen phlegm (sputum) and bronchial secretions".

(4) "Helps drainage of the bronchial tubes by thinning the mucus".

(5) "Relieves irritated membranes in the respiratory passageways by preventing dryness through increased mucus flow".

b. *Warnings.* (1) "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(2) "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a physician".

(3) *"Caution:* A persistent cough may be a sign of a serious condition. If cough

persists for more than 1 week, tends to recur or is accompanied by high fever, rash or persistent headache, consult a physician".

2. *Category II conditions under which expectorant ingredients are not generally recognized as safe and effective or are misbranded.* The use of expectorants under the following conditions is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel concludes that the following ingredients and labeling should be removed from the market until scientific testing supports their use.

Category II Active Ingredients

The Panel has classified the following expectorant active ingredients as not generally recognized as safe and effective or as misbranded:

Antimony potassium tartrate
Chloroform
Iodides: Calcium iodide anhydrous, Hydriodic acid syrup, Iodized lime, Potassium iodide
Ipecac fluidextract
Squill preparations: Squill, Squill extract
Turpentine oil (spirits of turpentine) (oral)

a. *Antimony potassium tartrate.* The Panel concludes that antimony potassium tartrate is not safe for OTC use as an expectorant.

(1) *Safety.* Antimony potassium tartrate is not safe in the dosage range used as an expectorant.

The trivalent salts of antimony are potent inducers of vomiting; they act on centers in the brain as well as locally on the stomach walls. Because the antimony ingredient in this preparation tends to accumulate in the body and not to be excreted in a manner similar to arsenic, the danger of toxic reactions increases with repetitive or chronic use. These toxic reactions consist of marked irritation of the stomach and intestinal mucosa. Pain in joints and muscles are common, and the muscles of the heart may be depressed. Abdominal pain, rash and vascular collapse as well as a number of cases of hemolytic anemia, some fatal, have been reported (Ref. 1). Such toxic effects have been seen with the use of the trivalent compound at higher doses for the treatment of helminthic infections; but even in doses suitable for expectorant activity, antimony potassium tartrate is considered too toxic because of its cumulative properties to be used as an OTC product (Ref. 1).

(2) *Effectiveness.* There is no evidence that antimony potassium tartrate is effective as an expectorant.

When administered in subemetic doses, antimony potassium tartrate theoretically exerts its expectorant activity through reflex stimulation of the salivary and bronchial glands (Ref. 2). There is, however, not one documented study in either animals or man demonstrating its effect on cough, sputum production or respiratory tract secretions (Ref. 3).

(3) *Evaluation.* Because of its toxicity and tendency to accumulate in the body, the Panel is of the opinion that even subemetic doses present risks which outweigh whatever benefit theoretically might occur since there is no evidence to support effectiveness.

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(2) "Drill's Pharmacology in Medicine," 2d Ed., Edited by DiPalma, J. R., McGraw-Hill, New York, p. 689, 1958.

(3) OTC Volume 040190.

b. *Chloroform.* The Panel concludes that chloroform is not effective for OTC use as an expectorant. The Panel is aware that the safety of chloroform is being questioned at present and has therefore limited its use only as a flavoring agent in CCABA preparations.

(1) *Safety.* The Panel concludes that the question of safety is dependent on dosage and abuse potential.

In doses of 4 to 8 ml orally, chloroform has been known to produce a narcotism similar to that occurring when administered by inhalation but developing more slowly and of longer duration (Ref. 1). The mean lethal dose by ingestion is approximately 30 ml (Ref. 2), although as little as a teaspoonful has produced serious illness. Symptoms of toxicity due to chloroform ingestion are often delayed for 2 or more days (Ref. 3). The problem of abuse at a "chloroform party" has recently been reported (Ref. 4).

Three documents concerning the safety of chloroform were submitted to the Panel for review and appropriate action. These pertained to the possible carcinogenicity of chloroform (Refs. 5 and 6) and the acute toxicity of chloroform in rats with an extrapolation to a suggested "maximum permissible limit" in humans (Ref. 7).

The first document was a review of a report by Harris on the implications of cancer causing substances in Mississippi River water (Ref. 5). A detailed analysis of the epidemiological data, presented together with a review of the statistical methods and the animal studies, is reported in full in the minutes of the 17th meeting of the Panel, Appendix 9 (Ref. 8). The Panel recognizes that there are serious inconsistencies in the report which makes the extrapolation of the data to possible risks of cancer from chloroform in drinking water unacceptable. Furthermore, the evidence of carcinogenicity in mice is conflicting and inconclusive and its extrapolation to another species, man, is open to serious question. Accordingly, the Panel concludes that for the report pertaining to the possibility of chloroform being a carcinogen in drinking water there is no evidence to support this possible carcinogenic hazard in the recommended dosages. This view is supported by an ad hoc Study Group on "Assessment of Health Risk from Organics in Drinking Water" in their report to the Hazardous Materials Advisory Committee of the Environmental Protection Agency (Ref. 9).

The second document (Ref. 7) attempts to establish some guidelines on permissible limits of solvent residues in chemicals. The authors list the obvious limitations of their study, i.e., the difficulty of extrapolating from rat to man; an acute single dose study does not provide an answer regarding the effect of chronic exposure; and the questionable use of arbitrary conversion factors that have no scientific basis. Their revised figure for the permissible limit for chloroform is 0.25 ml/60 kg. The Panel's recommended concentration of 0.4 percent by volume is therefore well within the authors' suggested permissible limit. The Panel recommends that chloroform be available only as a flavoring agent at a maximum concentration of 0.4 percent which represents 0.004 ml/ml or 0.02 ml/5 ml (teaspoon) of a product dosage. This is well within their revised permissible limit of 0.25 ml/60 kg. of body weight.

The third document is a preliminary report from the National Cancer Institute entitled, "Report on Carcinogenesis Bioassay of Chloroform" dated February 1976 (Ref. 6). The protocol consisted of a total of 400 rats and mice with suitable control animals receiving daily doses of chloroform orally for a total of 546 days. The treated animals were divided into low and high dose groups.

For rats, the results of the study showed a decreased survival rate which appeared dose related. Clinical evidence of toxicity appeared during the first 10 weeks but became more apparent during the second year of the study. The control groups also showed these signs by the 70th week. Transient palpable nodules were noted in both test and control groups by the end of the second year. The incidence of "all tumors" in both treated and control rats did not differ. Significant differences from control groups occurred with kidney tumors in male rats which appeared dose related and thyroid tumors in the female rats but the thyroid tumors were not considered relevant to the study because of the known incidence of spontaneously occuring thyroid tumors in this strain of rat. Neoplastic nodules of the liver occurred with equal frequency in test and matched controls (5 percent). Necrosis of hepatic parenchyma occurred with slightly greater frequency in the chloroform-treated rats.

For mice, results of the study showed that there were no significant differences in survival rate between the controls and treated mice except for the high dose female group. Beginning after 42 weeks of treatment, the chloroform-treated mice began to exhibit a bloated appearance with abdominal distention. The incidence of "all tumors" in the treated groups was significantly higher, and this was solely due to the presence of hepatocellular cancer.

The conclusions to be drawn from this study are that orally administered chloroform can produce hepatic neoplasms in this strain of mice when administered at these levels and for a prolonged period of time. There was a less striking correlation of kidney tumors with chloroform ingestion in the rat species. But the lack of any increase in hepatic tumors in the rats or kidney tumors

in the mice is attributed by the authors as illustrating "species differences in organ specificity and sensitivity." The Panel questions whether this then can be extrapolated to other species such as dog or man.

The Panel has considered the dosage of chloroform administered in the study. The average 400-gm rat received 36 to 80 mg/day for 546 days or a total of 19.656 to 43.680 gm. The average 30-gm mouse received 4 to 14 mg/day for 546 days or a total of 2.184 to 7.644 gm. In terms of an average 60-kg human, the equivalent doses would be 5.4 to 12.0 gm/day or a total of 2,984.4 to 6,552 gm for 546 days. If the mouse dosage is extrapolated, the human dose would be 8.0 to 28.0 gm/day or a total of 4,368 to 15,288 gm. The Panel finds that the use of chloroform as a flavoring agent at a maximum allowable concentration of 0.4 percent or 0.4 gm/100 ml would require the consumption of 1.35 to 7 liters/day for a total of 737.1 to 3,822 liters in 546 days. If the usual cough mixture is dispensed in a 120 ml bottle, this would represent the consumption of 31,850 bottles in a 2-year period. The Panel questions how many other drugs, food stuffs, flavoring agents, etc. would be toxic or even carcinogenic at these levels.

In the final analysis, the Panel is unable to determine from the available data the lack of safety of chloroform in man at the 0.4 percent concentration proposed for use as a flavoring agent. Obviously, there is a dose-response relationship with respect to toxicity and the potential for abuse exists just as with alcohol.

(2) *Effectiveness.* There is no evidence that chloroform is effective as an expectorant or that it ameliorates cough.

There is no documentation of the expectorant activity of chloroform. One report (Ref. 9) states that it is "probably harmless as well as useless in the dosages used." *The U.S. Dispensatory* reports that chloroform has been added to cough mixtures as a respiratory sedative, but its action is too fleeting to be of any great value (Ref. 1). *Remington's Practice of Pharmacy* (Ref. 10) classifies chloroform as a pharmaceutical necessity.

(3) *Evaluation.* The Panel concludes that chloroform should be restricted to use as a flavoring agent (pharmaceutical necessity) in amounts not to exceed 0.4 percent by volume in an OTC CCABA product.

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c. *Iodides (calcium iodide anhydrous, hydriodic acid syrup, iodized lime, potassium iodide).* The Panel concludes that the iodides are neither safe nor effective for OTC use as expectorants.

(1) *Safety.* At a dosage that may be effective, iodides are not considered safe as OTC preparations.

The action and toxic effects of these compounds are due to the iodide content. The iodides are readily absorbed from the gastrointestinal tract and concentrated primarily in the secretions of the respiratory tract. The Panel is unaware of any animal studies on the safety of the iodides. There are no controlled studies on short-term use of iodides as expectorants. The incidence of side effects and toxicities are directly proportional to the dose and duration of therapy, and practically all persons continually treated with high doses will manifest symptoms of iodism which may simulate the symptoms of the "common cold". Some individuals, though not frequently, are highly sensitive to iodides and will react to the first few doses with serious consequences (Ref. 1). The clinical experience with iodides has been mostly in the treatment of chronic diseases, such as bronchial asthma, chronic bronchitis, bronchiectasis and emphysema; therefore, most of the toxicity has been related to chronic administration. The effective dose is 900 mg daily in divided doses (Refs. 2 and 3). Leonardy (Ref. 4) estimates the optimal dose at 25 to 35 mg/kg daily in divided doses. At these doses, there is a high incidence of toxic effects varying in seriousness from mild iodism to generalized papulovesicular eruptions, hypothyroidism, edema of the glottis, submandibular adenitis (Ref. 1), and iodide fever (Ref. 5).

Murray and Stewart (Ref. 6) reported two cases of iodide goiter and found at least 170 cases in the literature as well as several other cases through personal communications. Carswell, Kerr and Hutchison (Ref. 7) reported iodide-induced goiters in the fetuses of pregnant women. Two cases of neonatal death apparently due to congenital goiter caused by iodides compressing the trachea are reported by Galina, Avnet and Einhorn (Ref. 8). Continued heavy use in children and adults may produce goiter and/or hypothyroidism (Refs. 9 and 10). *The Medical Letter* (Ref. 11) discusses the hazards of drug-induced goiters and cites iodides as the most frequent cause. The blood levels needed to induce goiter could not be established. Falliers et al. (Ref. 2), in a double-blind crossover study of 52 asthmatic children, found a high incidence of adverse effects. One child could not complete the study because of the development of a severe generalized papulovesicular eruption. Sixteen adolescents developed acne-form lesions. Eighteen showed thyroid enlargement but no evidence of suppressed thyroid functions. Leonardy (Ref. 4), in discussing the use of iodides in the treatment of bronchial asthma, cites a review by Peacock and Davison (Ref. 12) of 500 cases in which 13.5 percent of patients receiving iodides had sufficient side effects to warrant discontinuing the drug.

There is a wide variety of diseases which contraindicate the use of iodides or require caution that the consumer does not have the expertise to determine, such as hypersensitivity to iodides, thyroid disease, psoriasis (Refs. 3 and 13) and various types of dermatoses.

Because of the high incidence of untoward effects and the potential for toxicity, iodides should be used only under the advice and supervision of a physician.

(2) *Effectiveness.* Iodides may be effective as an expectorant when given in adequate doses in some chronic respiratory disease. There is no evidence that they are efficacious in acute upper respiratory infections.

Animal studies have demonstrated the presence of iodides in the respiratory tract fluid (RTF) and an increase in the amount of RTF or a decrease in its viscosity (Refs. 14 and 15). Numerous investigators have reported observations on the expectorant action of iodides (Ref. 14). Many cite the rapid appearance of iodides in the RTF after the administration (Refs. 16, 17, and 18). The mechanism of the action of iodides as expectorants is not clear. Their presence in the RTF does not necessarily indicate increased amounts of RTF or decreased viscosity. It has been suggested by Lieberman and Kurnick (Ref. 19) that the iodides may liquefy purulent sputum by inducing the enzymatic hydrolysis of proteins. In asthmatics, no consistent change in viscosity resulting from iodides was reported by Leonardy (Ref. 4), citing as evidence a number of studies. Hirsh et al. (Ref. 20), using a new technique to measure viscosity, have been able to obtain consistent and reproducible results, but no final answer is yet available.

Falliers et al. (Ref. 2), in a 3-year double-blind study of 52 children with chronic asthma, demonstrated a statistically significant improvement in the children receiving potassium iodide 300 mg 3 times daily. The population receiving iodides improved but there was a wide variability in the response of the individuals in the study, and there is no an-

swer to why. It may be due to some other property than that of its expectorant property.

While the iodides are possibly expectorants, there are insufficient studies to confirm this. This would suggest the need for more controlled studies and better techniques for evaluation of the action of iodides.

(3) *Evaluation.* The Panel concludes that iodides are not safe for OTC use. Because of the wide variety of diseases which contraindicate their use and because of the potential for toxicity and untoward effects, iodides should be used only under the advice and supervision of a physician.

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d. *Ipecac fluidextract.* The Panel concludes that ipecac fluidextract is not safe for OTC use as an expectorant.

(1) *Safety.* Based on its long history of use, it is generally accepted that syrup of ipecac is safe although no studies can be found to substantiate this belief (Ref. 1). The fluidextract of ipecac, however, is 14 times more potent than the syrup (Ref. 2) possessing a 2 percent total alkaloidal content. The chief alkaloids of ipecac are emetine and cephaeline varying in ratio from equal parts to a fourfold preponderance of emetine. These alkaloids are responsible for its therapeutic and toxic manifestations (Ref. 3).

Toxic, even fatal doses may occur in man at 2 oz of the fluidextract. A dose of 10 ml produced death in a 4-year-old child (Ref. 4). Death from the ingestion of the syrup has not been reported. However, it is believed that many cases of overdosage result from mistaking the fluidextract for the syrup. Toxic manifestations of overdosage include nausea, bloody stools, and vomitus, cramping, and abdominal pain. Myocardial manifestations have also been reported (Ref. 3).

The Panel is aware of a reference to an expectorant dose of the fluidextract of 0.2 to 0.5 ml (Ref. 5), however the Panel feels that the syrup possesses a superior benefit-to-risk ratio and that ipecac fluidextract should not be available for OTC use as an expectorant.

(2) *Effectiveness.* Ipecac fluidextract has both local and central effects; however, there are no acceptable clinical studies to substantiate its use as an expectorant.

(3) *Evaluation.* The Panel is unable to determine a safe dose for ipecac fluid extract for use as an expectorant. Because of its documented toxicity and since there is no evidence to support effectiveness, the Panel concludes that ipecac fluidextract is not safe for use as an expectorant.

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e. *Squill preparations (squill, squill extract).* The Panel concludes that squill preparations are not safe or effective for OTC use as expectorants.

(1) *Safety.* Squill is a toxic substance capable of causing nausea, vomiting, and violent purging. It contains scillarin A and scillarin B, glycosides that may be toxic to the heart. The powdered drug and extracts from it have been used as rat poison. As a rat poison, red squill is usually preferred but all squill preparations have the same general properties (Ref. 1). Although the market experience would indicate that squill is probably safe, the doses used are small and there are no data available to relate this dose to effectiveness or to the lower limits of toxic doses (Ref. 2). Available information relates to sources and methods for preparation. The lowest toxic dose is currently estimated at 50 mg/kg (Ref. 3).

(2) *Effectiveness.* Squill is an irritant to the gastric mucosa and produces a reflex expectorant action. In larger doses it is an emetic (Refs. 1, 4, and 5). There are no available data to relate these effects to dose. Squill is practically always given as one of several drugs in various preparations and there are no data to indicate whether it does or does not contribute to the expectorant action of the preparation.

(3) *Evaluation.* Because of its known toxicity and historical use as a rat poison, and since there are no data available to relate marketed doses as an expectorant to the lower limits of toxic doses, the Panel is of the opinion that the risks outweigh whatever benefit might occur. Therefore, the Panel concludes that squill preparations are not safe or effective for OTC use.

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f. *Turpentine oil (spirits of turpentine) (oral).* The Panel concludes that oil of turpentine is not safe for OTC use when taken orally as an expectorant.

(1) *Safety.* Oil of turpentine is a volatile oil distilled from turpentine, an oleoresin obtained from the pine tree. It has a characteristic odor and taste. The substance has been administered orally, topically and by inhalation.

In doses of 15 ml in children and 150 ml in adults fatal poisoning may occur (Ref. 1). Excessive oral doses produce marked irritation of the alimentary tract, especially of the stomach and of the pelvic organs. Toxic symptoms include vomiting, diarrhea, acute pain,

renal irritation, bloody stools and hyperemia of all abdominal organs. Continued oral use may lead to cloudy swelling and fatty degeneration of the liver. Abnormal central nervous system symptoms may develop (Refs. 2 and 3).

Since no safe oral dose has been established for effective use as an expectorant, the Panel concludes that turpentine oil should not be available for oral OTC use as an expectorant. However, elsewhere in this document, the Panel concludes that the ingredient is safe when applied topically or used as an inhalant but that there are insufficient data to permit final classification of its effectiveness for inhalant or topical use as an expectorant. (See part IV. paragraph B.3.n. below—Turpentine oil (spirits of turpentine) (topical/inhalant).)

(2) *Effectiveness.* Oil of turpentine is irritating and its chief suggested uses are based on this property (Refs. 1 and 4). There is no evidence to support its effectiveness as an expectorant when taken orally.

(3) *Evaluation.* The Panel is unable to determine a safe oral dose for turpentine oil for use as an expectorant. The Panel is of the opinion that the risk from oral administration outweighs whatever benefit might occur. Therefore, the Panel concludes that turpentine oil is not safe for oral use as an expectorant.

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Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety and/or effectiveness of the product are unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel has previously discussed such labeling. (See part II. paragraph O. above—CCABA Product Labeling Claims Not Supported by Scientific Evidence.) However, labeling that is descriptive of the product such as its taste or appearance are acceptable.

The Panel concludes that the following claims are misleading and are unacceptable for preparations used as expectorants. These and similar claims are unsupported by scientific data. The term "congestion", which may be interpreted by the target population to denote a discomfort of the chest, may result from a variety of causes, several of which may be of a most serious nature and require professional attention. Other terms and phrases are descriptive, but vague, and cannot be scientifically evaluated. Statements or phrases which allude to greater potency or suggest superiority of a product are not acceptable.

All claims that state or imply a therapeutic action or safety property peculiar to the preparation that cannot be demonstrated in controlled studies are not acceptable, e.g., "specially formulated", "improved", "selected", "natural", "extra strength", "teamed components", "superior to ordinary", "modern", and "superior".

Claims implying a physiological effect that has no foundation or meaning or will be meaningless to the public are unacceptable; such as "antiallergic", "gets at the roots of", "fights", "wakes up", "recommended by doctors", "multiaction", and "travels through the blood stream", "works internally", and "actively moistens".

Claims for relief where time is indeterminate and not supported by scientific data are unacceptable, such as "fast" and "prompt". Using the above criteria the Panel feels that the following specific claims are unacceptable:

a. *Unacceptable claims because of vagueness and the inability to evaluate them scientifically.* (1) "Temporarily relieves cough congestion by working internally to break up phlegm".

(2) "Help decongest bronchial passage".

(3) "To help clear congestion".

(4) "Frees secretions along lower respiratory tract".

(5) "Helps loosen congestion so you can cough it up and get it off your chest".

(6) "Works internally".

(7) "Actively moistens the bronchial lining".

(8) "Soothes tired throats".

(9) "Promotes free breathing".

(10) "Restores free breathing".

(11) "Eases breathing".

b. *Unacceptable because the claims allude to greater potency or suggest superiority of a product which is not supported by scientific data.* (1) "Full expectorant".

(2) "Combines modern expectorant".

(3) "Superior expectorant".

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel concludes adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed conditions listed below. Because of the lack of suitable objective criteria for evaluating expectorant activity and the need to rely on subjective assessment of highly variable symptoms, the Panel believes it reasonable to provide 5 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within 5 years, however, the conditions listed in this category should no longer be marketed as over-the-counter products.

Category III Active Ingredients

The Panel has concluded that the available data are insufficient to permit final classification of the following claimed expectorant active ingredients:

Ammonium chloride
Beechwood creosote
Benzoin preparations (inhalant): Compound tincture of benzoin, Tincture of benzoin
Camphor (topical/inhalant)
Eucalyptol/eucalyptus oil (topical/inhalant)
Glyceryl guaiacolate
Ipecac syrup
Menthol/peppermint oil (topical/inhalant)
Pine tar preparations: Extract white pine compound, Pine tar, Syrup of pine tar, Compound white pine syrup, White pine
Potassium guaiacolsulfonate
Sodium citrate
Terpin hydrate preparations: Terpin hydate, Terpin hydrate elixir
Tolu preparations: Tolu, Tolu balsam, Tolu balsam tincture
Turpentine oil (spirits of turpentine) (topical/inhalant)

a. *Ammonium chloride.* The Panel concludes that ammonium chloride is safe in the dosage range used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that ammonium chloride is safe in the dosage ranges used as an expectorant.

Several studies have documented the occurrence of severe acidosis, especially in patients with renal or hepatic dysfunction (Refs. 1 through 3). Most of these occurred with doses in excess of 6 to 8 gm per day where it was being used as a diuretic. Relman, Shelburne and Talman (Ref. 4) reported two near fatal cases following ingestion of huge amounts, 82 gm taken in a 48 hour period; while Ticktin, Fazekas and Evans (Ref. 5) described a case report of hepatic coma precipitated by 6 gm in a patient with congestive heart failure. At the dose ranges of 250 to 500 mg 4 to 6 times daily, which is the customary dose as an expectorant, the major adverse reaction has been nausea and emesis (Ref. 6).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of ammonium chloride as an expectorant. No objective evaluations have been reported. Partially controlled subjective studies (Ref. 7) showed no significant change in either sputum volume or viscosity. Several investigators (Refs. 8 through 10) felt that sputum was more fluid and easier to raise when given at doses 0.3 gm every 2 hours, and Basch, Holinger and Poncher (Ref. 11) reported a decrease in visocity and pH (acidity) in patients with damaged bronchial tubes and infection.

(3) *Proposed dosage.* Adult oral dosage is 300 mg every 2 to 4 hours. Children 6 to under 12 years oral dosage is 150 mg every 2 to 4 hours. Children 2 to under 6 years oral dosage is 75 mg every 4 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warnings.* (i) "*Caution:* This product must be taken with adequate amounts (½ to 1 glass) of fluids with each dose".

(ii) "Do not take this product if you have heart trouble or chronic kidney or lung disease except under the advice and supervision of a physician".

(5) *Evaluation.* Data to demonstrate effectiveness as an expectorant will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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b. *Beechwood creosote.* The Panel concludes that beechwood creosote is safe in the dosage range used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that beechwood creosote in the usual dosages contained in lozenges or cough mixtures for expectorant activity is safe.

Creosote is a distillate of wood tar and has a smokey color and a pungent taste. Dosages in excess of 4 gm 3 times daily produces giddiness, dimness of vision, circulatory collapse, convulsions and coma (Ref. 1). Because of the taste, it is normally given well-diluted (Ref. 2). Occasional adverse gastrointestinal side effects are mentioned in one report but are poorly documented (Ref. 3). Based on the available data and the presence of beechwood creosote on the market for many years, the Panel concludes that this ingredient is safe for OTC use.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of beechwood creosote as an expectorant. No controlled or partially controlled studies were submitted to the Panel documenting its effectiveness as an expectorant. Only one reference (Ref. 3) was found that reported some increase of respiratory tract fluid (RTF) in animals given high dosages but the authors expressed doubt as to the applicability of these data to man. According to the standard compendia (Refs. 1 and 4), an average dose of beechwood creosote is 250 mg 3 or 4 times a day. In the two submissions to the Panel listing creosote, the dosages are 3.29 mg/lozenge and 33 mg/15 ml every 3 hours (Ref. 5). This 40 to 80-fold difference in dosage (3.29 mg/lozenge, 8 dosages daily) appears illogical and there is no evidence to indicate that creosote is effective in such low doses. The Panel concludes that further studies are needed to determine effectiveness.

(3) *Proposed dosage.* Adult oral dosage is 250 mg every 4 to 6 hours not to exceed 1,500 mg in 24 hours. Children 6 to under 12 years oral dosage is 125 mg every 4 to 6 hours not to exceed 750 mg in 24 hours. Children 2 to under 6 years oral dosage is 62.5 mg every 4 to 6 hours not to exceed 375 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness as an expectorant will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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c. *Benzoin preparations (compound benzoin tincture, tincture of benzoin) (inhalant).* The Panel concludes that tincture of benzoin and compound benzoin tincture are safe in the dosage ranges used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that benzoin tincture and compound benzoin tincture are safe in the dosage ranges used in boiling water as a steam inhalant for expectorant purposes.

Benzoin is the balsamic resin obtained from *Styrax benzoin* Dryander or Styrax paralleloneurus Perkins, known in commerce as Sumatra Benzoin or from *Styrax* tonkinensis (Pierre) Craib ex Hartwich, or other species of the Section *Anthostyrax* of the genus Styrax, known in commerce as Siam benzoin (San. *Styraceae*) (Ref. 1).

Benzoin is used in preparing official preparations, e.g., compound benzoin tincture, United States Pharmacopeia XIX (Ref. 1) and benzoin tincture, National Formulary XI (Ref. 2). Compound benzoin tincture contains 74 to 80 percent alcohol and is prepared by a maceration process incorporating benzoin, aloe, storax and tolu balsam using alcohol as a menstruum (Ref. 1). Benzoin tincture contains 75 to 83 percent alcohol and is also prepared by macerating benzoin, the final product being a 20 percent solution of benzoin (Ref. 2). These preparations are used topically as a protectant and antiseptic and by steam inhalation as an expectorant (Refs. 3 and 4). It is generally recognized as safe when administered by steam inhalation in accordance with recommended concentrations. The alcohol content would be responsible for the major toxic signs and symptoms arising from oral administration of the tincture (Ref. 5).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of tincture of benzoin and compound benzoin tincture as an expectorant.

Although compound benzoin tincture and benzoin tincture have been advocated and used for generations as a component of steam inhalations to promote an expectorant action, no studies demonstrating this effect have been found in the literature or OTC submissions.

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years of age is as follows: Add 1 teaspoonful of compound benzoin tincture or benzoin tincture to a pint of water in a hot steam vaporizer, bowl or washbasin. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV, paragraph B.I. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warning:* "For use by steam inhalation only. Do not take by mouth".

(5) *Evaluation.* Data to demonstrate effectiveness as an expectorant will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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d. *Camphor (topical/inhalant)*. The Panel concludes that camphor is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an expectorant.

(1) *Safety*. Clinical experience has confirmed that camphor (topical/inhalant) is safe in the dosage ranges used as an expectorant.

Camphor is a local irritant producing skin redness when rubbed on the skin. However, when not vigorously applied, it may produce a feeling of coolness on the skin as does menthol. It acts similarily on the respiratory tract. Taken orally in small doses it produces a feeling of warmth and comfort in the stomach but in larger doses it is irritating and can cause nausea and vomiting. Camphor also has a mild local anesthetic action and its application to the skin may be followed by numbness. The systemic effects are primarily related to stimulation of the central nervous system. The ingestion of solid camphor by children can cause convulsions (Ref. 1). As little as 0.75 gm of camphor equivalent to a teaspoonful of liniment of camphor or camphorated oil that contains 20 percent camphor has been fatal to a child. Commercially available ointments containing mixtures of volatile substances for use as decongestants or antitussives contain about 5 percent camphor. Since it is conceivable that ingestion of a sufficient amount of such a preparation could produce toxic effects in a young child, a suitable warning should be present on the label. The ingestion of 2 gm of camphor generally produces toxic effects in an adult although up to 1.5 oz has been ingested with recovery (Ref. 2).

(2) *Effectiveness*. There are no well-controlled studies documenting the effectiveness of camphor (topical/inhalant) as an expectorant. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

A standard text indicates that camphor may have a slight expectorant action (Ref. 1). Well-controlled specific studies to document this effect have not been found in the literature.

(3) *Proposed dosage*. Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 5 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapor rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 7 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl, or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 0.02 to 15 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling*. The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning*: "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning*: "For steam inhalation only. Do not take by mouth".

(5) *Evaluation*. The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below— Data Required for Evaluation.)

(iii) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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e. *Eucalyptol/eucalyptus oil (topical/inhalant)*. The Panel concludes that eucalyptol/eucalyptus oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an expectorant.

(1) *Safety*. Clinical experience has confirmed that eucalyptol/eucalyptus oil (topical/inhalant) is safe in the dosage ranges used as an expectorant.

Eucalyptus oil is about 70 percent active eucalyptol. Fatalities have followed doses of the oil as small as 3.5 ml although recovery has occurred after doses of 20 and even 30 ml. Symptoms include epigastric burning with nausea and vomiting, vertigo, ataxia, muscle weakness and stupor (Refs. 1 and 2). A study of 223 subjects in which an ointment containing several volatile substances, including eucalyptus oil 1.3 percent, was applied for 48 hours to areas of intact skin under a patch and to abraded skin, revealed no instances of irritation, inflammation, wheal or hives following the period of exposure (Ref. 3). A study of ten subjects who received application of an ointment containing several volatile substances including eucalyptus oil 1.3 percent to their trunks 3 times daily for 3 weeks, then 1 week off followed by another 1 week of treatment, revealed no local reactions during this subsequent challenge phase (Ref. 4). A study of infants and children with respiratory infection who received an ointment containing a mixture of volatile oils, including eucalyptus oil 1.3 percent, applied to the chest and neck demonstrated no adverse effect from inhaled vapors by that route of administration on the rate of clearing of laryngeal edema (Ref. 5). In another study, the vapors were produced by placing a liquid mixture of volatile substances, including eucalyptus oil 1.7 percent, in the water of a hot steam vaporizer and administered via inhalation. Exaggerated use studies in adults and children, i.e., exposure for several hours to higher than recommended exposure concentrations either due to sitting in closer proximity to the vaporizer or placing 2 to 5 times the recommended dose of the volatile substance in the vaporizer, were not associated with irritating or toxic effects (Refs. 6 and 7).

A series of studies assessing buccal safety and overt side effects from lozenges containing a mixture of volatile oils was conducted in over 300 subjects (Refs. 8 through 11). Lozenges containing up to 5.5 mg eucalyptus oil were dissolved in the mouth every hour for 8 hours on 2 successive days. Mild erythema of the buccal mucosa and tongue was observed but did not differ appreciably from the response to dissolving lozenge sugar base without volatile oils. Incidence of gastrointestinal symptoms did not differ from control either (Refs. 8 through 11).

An aerosolized dosage form of volatile substances including 1 percent eucalyptus oil has also been utilized for treatment of nasal congestion. In humans, such aerosol sprays have been generally safe when used as directed but there have been reports of deaths from deliberate sniffing abuse, particularly when the subject inhales from a plastic bag into which the material has been sprayed (Ref. 12). Furthermore, one commercial preparation containing a particular solvent (1,1,1-trichloroethane) was recently recalled from the market due to potential hazards of this substance (Ref. 13).

(2) *Effectiveness*. There are no well-controlled studies documenting the effectiveness of eucalyptol/eucalyptus oil (topical/inhalant) as an expectorant. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

Eucalyptus oil is traditionally assumed to have an expectorant action by virtue

of direct stimulation of bronchial secretory cells following inhalation (Ref. 14). In one study, eucalyptus oil was administered via steam inhalation to rabbits and respiratory tract fluid collected (Ref. 15). At normal doses eucalyptus oil did not increase the volume or decrease the specific gravity of the collected fluids. Larger doses were required for eucalyptus oil to produce this effect, and these doses led to local inflammation and several animal deaths (Ref. 15). In a later study, this group administered eucalyptol by stomach tube to anesthetized animals. Eucalyptol was shown to be an expectorant in rats, guinea pigs, rabbits, cats, and dogs. The effect was not influenced by section of the afferent gastric nerves. From this observation the authors concluded that eucalyptol does not act by a reflex mechanism in the stomach but directly upon the secretory cells of the respiratory tract (Ref. 16). Conclusive studies to confirm this expectorant property in humans are lacking.

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 1.3 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 1.7 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 0.2 to 15.0 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations: (1) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

(iii) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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f. *Glyceryl guaiacolate.* The Panel concludes that glyceryl guaiacolate is safe in the dosage ranges used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that glyceryl guaiacolate is safe in the dosage ranges used as an expectorant.

Acute and chronic toxicity studies in animals demonstrated no adverse pathologic findings (Ref. 1). A number of studies in humans also demonstrates the safety of glyceryl guaiacolate over a wide range of dosages (Refs. 2, 3, and 4). Carter (Ref. 5) administered 100 mg/lb of body weight to 18 children with cerebral palsy for periods of 1 month. One child complained of loss of appetite and two exhibited nausea and vomiting. All laboratory data remained within normal limits (blood chemistry, complete blood count, and urine). An epidemiological study (Ref. 6) indicates that glyceryl guaiacolate is one of the most widely used medications with few reported adverse reactions.

Inhibition of in vitro platelet aggregation in the blood with prolongation of coagulation time of activated plasma has been described (Refs. 7 and 8) but appears to have no clinical significance (Refs. 9 and 10). Glyceryl guaiacolate may interfere with certain laboratory tests, such as 5-hydroxyindoleacetic acid and vanillyl mandelic acid (Refs. 11 and 12) which are employed as screening tests for carcinoid (hormone secreting) tumors and pheochromocytoma.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of glyceryl guaiacolate as an expectorant.

Earlier animal studies, in which glycerol guaiacolate was reported as increasing respiratory tract fluid (Refs. 13 and 14) were subsequently revised to indicate that the expectorant activity of glyceryl guaiacolate occurred only at extremely high doses (Ref. 15).

There have been a large number of clinical studies in man. Even in the early studies, the lack of acceptable standard techniques for evaluation was recognized. These studies can be subdivided into subjective uncontrolled reports (Refs. 16, 17, and 18) claiming effectiveness in the management of cough and good patient acceptance; subjective controlled or semicontrolled studies (Refs. 19 and 20) claiming superiority of glyceryl guaiacolate (100 to 200 mg 4 times daily) over placebo with respect to ease of raising sputum, and ameliorating the unproductive cough and objective controlled studies in which the flow properties of sputum were measured or the clearance rates of inhaled radioactive tracer particles were determined. Hirsch et al. (Ref. 2) and Hirsch, Viernes and Kory (Ref. 21) found glyceryl guaiacolate at dosages of 800 to 1,600 mg daily to be no more effective than placebo in lowering sputum consistency, increasing sputum volume or improving ventilatory function. The subjective ease of expectoration was also no different than with placebo. Chodosh (Ref. 22) and Chodosh, Medici and Enslein (Ref. 23), on the other hand, dispute these findings and in a letter to the editor of *Chest*, Chodosh and Medici (Ref. 24) claim improvement in subjective symptoms, pulmonary function tests, and sputum stickiness (adhesiveness) with 2.4 gm glyceryl guaiacolate daily. Perhaps the most striking point in his discussion is that even at 2.4 gm daily the most significant changes were noted only after 10 days

although trends could be detected at 7 days. The report by Thomson, Pavia and McNicol (Ref. 25) showing a significantly faster clearance of inhaled radioactive particles over the first 5 hours with glyceryl guaiacolate in single doses of 200 mg as compared to placebo in bronchitic patients in a double-blind crossover study is of special interest both in the evaluation of glyceryl guaiacolate and as an objective type of assessment for expectorant drugs. This is a new approach to the study of expectorants and is objective in design. If results can be confirmed, it may represent a "breakthrough" in methodology.

If glyceryl guaiacolate requires 7 to 10 days to begin to demonstrate a significant expectorant effect, it is obviously not suited for OTC use where rapid relief of symptoms in a self-limited illness of relatively short duration is desired. It should be emphasized that the study by Thomson, Pavia and McNicol (Ref. 25) suggesting drug activity is a single study that has not been confirmed by any other investigator. Hirsch et al. (Ref. 2) and Hirsch, Viernes and Kory (Ref. 21), employing another objective controlled method of study, were unable to demonstrate effectiveness. It would appear that the contradictory results of these two studies cancel each other out in a manner of speaking.

A recent subjective double-blind study was submitted in which there were 121 patients in a placebo group and 118 who received 200 mg every 6 hours for a period of 72 hours (Ref. 26). Statistical analysis of the data was reported as showing a significant reduction in cough frequency and intensity in the patients on glyceryl guaiacolate. However, this conclusion by a subjective method of evaluation is unacceptable as a claim for suppression of cough frequency or intensity in keeping with the Panel's statement that effectiveness of a drug with respect to antitussive activity must be assessed by objective techniques, such as cough-counting methods as described in the section under evaluation of antitussives. (See part III. paragraph C. below—Data Required for Evaluation.)

In addition, this study reported that glyceryl guaiacolate administration was associated with the production of a significantly thinner sputum and was effective in increasing sputum volume and facilitating the raising of secretions in patients with a productive cough. In examining the data, it was noted that one investigator in this multidisciplinary study submitted two separate studies with a total of 76 subjects which accounted for approximately one-third of the total subject population. Another investigator presented data that showed no significant difference from placebo and a third investigator showed a significant trend in favor of glyceryl guaiacolate. Because of the conflicting results of the different investigators on this study and the likelihood that the data from the single investigator referred to above would bias the results of the study when all the information is pooled, serious questions are raised as to the validity of the study. Retrospective analysis of the data with respect to smoking showed that there was no bias introduced by the incidence of smoking of the subjects (Ref. 27).

There are a number of controlled, objective studies with combinations of theophylline and glyceryl guaiacolate in reversible airway obstruction studies but these were not relevant to its expectorant acivity.

There is considerable dispute as to the effective dosage. From the more recent reports in the literature it would appear to be 2 to 4 times higher than the customary dose of 100 mg.

(3) *Proposed dosage.* Adult oral dosage is 200 to 400 mg every 4 hours not to exceed 2400 mg in 24 hours. Children 6 to under 12 years oral dosage is 100 to 200 mg every 4 hours not to exceed 1200 mg in 24 hours. Children 2 to under 6 years oral dosage is 50 to 100 mg every 4 hours not to exceed 600 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. Effectiveness to be established by only one additional controlled study which in view of the difficulty in obtaining objective criteria for such evaluations, could be a well-designed subjective study. (See part IV. paragraph C. below—Data Required for Evaluation.)

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(27) OTC Volume 040280.

g. *Ipecac syrup.* The Panel concludes that ipecac syrup is safe in the dosage ranges used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that syrup of ipecac is safe in the dosage ranges used as an expectorant but there are no known studies to substantiate this belief. There are no known studies on the toxicity of ipecac as a single ingredient. The chief alkaloids of ipecac, emetine and cephaeline, are very toxic (Ref. 1). It has been shown that when these alkaloids are given parenterally (by injection), they are cumulative with toxic effects on the heart, liver, kidney, intestinal tract, and skeletal muscle (Refs. 1 and 2); however,

when given orally, there is no information on the absorption of small doses from the gastrointestinal tract, or on the cumulative effects of repeated administration. In view of possible cumulative effects from oral administration, the Panel recommends a 1-week time limit of use for any ipecac preparation except when given under the advice and supervision of a physician.

Based on the long history of use and on the available data, the Panel concludes that when given in small doses as proposed below, ipecac syrup is safe for OTC use.

(2) *Effectiveness.* In large doses, ipecac is an emetic. However, in the subemetic dosages used as an expectorant, its effectiveness is questionable. There are no acceptable clinical studies to substantiate its use as an expectorant.

Practically all the work with ipecac was done more than 2 decades ago. Animal studies using varying preparations of ipecac indicate that this drug may increase the flow of respiratory tract fluid (Refs. 3 through 7). Several controlled studies in humans with chronic cough did not demonstrate that ipecac was effective as an expectorant (Refs. 8, 9, and 10). In one study, bronchial fluid collected by bronchoscopic drainage revealed lowered viscosity following ipecac administration (Ref. 11). The available data is insufficient to make a determination that ipecac is effective, and the Panel recommends further study.

(3) *Proposed dosage.* Adult oral dosage is 0.5 to 1 ml of a syrup containing not less than 123 mg and not more than 157 mg of total ether-soluble alkaloids of ipecac per 100 ml 3 to 4 times daily. Children 6 to under 12 years oral dosage is 0.25 to 0.5 ml of syrup 3 to 4 times daily. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warning:* "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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h. *Menthol/peppermint oil (topical/inhalant).* The Panel concludes that menthol/peppermint oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectivness for topical or inhalant OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that menthol/peppermint oil (topical/inhalant) is safe in the dosage ranges used as an expectorant.

Menthol is the chief constituent of peppermint oil, comprising not less than 50 percent. It may be obtained by distillation of the oil or by synthesis (Ref. 1). Toxic effects with an excess ingestion of peppermint oil or mentholated products can include abdominal pain, nausea, vomiting and symptoms of central nervous system depression, such as dizziness, staggering gait, slowed respiration, flushed face, sleepiness, and coma (Refs. 2 and 3). The fatal oral dose of menthol itself in man is about 2 gm (Ref. 4). Topically applied menthol produces a cooling sensation presumably due to stimulation of the cold sensory receptors, whereas higher concentrations have irritant properties. In one study, a 20 percent solution of menthol in oil rubbed on to the skin induced an intense and lasting cooling sensation followed by numbness with slight burning and skin redness. A 0.5 precent solution applied to the nasal or oral mucosa was subjectively irritating whereas a 0.2 percent solution was judged nonirritating (Ref. 5). A study of 223 subjects in which an ointment containing several volatile substances including menthol 2.8 percent was applied for 48 hours to areas of intact skin under a patch and to abraded skin revealed no instances of inflammation, wheal, hives, or primary irritation following the period of exposure (Ref. 6). Repeated topical application of mentholated products has been reported to give rise to hypersensitivity reactions, including contact dermatitis (Ref. 4). A study of ten subjects who received an application of an ointment containing several volatile substances including menthol 2.8 percent to their trunks 3 times daily for 3 weeks, then 1 week off, followed by another week of treatment, revealed no local reactions during this subsequent challenge phase (Ref. 7). One study suggests that the incidence of hypersensitivity to menthol appears to increase with increased duration of use. This survey revealed an incidence of less than 1 percent menthol hypersensitivity in 542 patients using a mentholated ointment for less than 10 years, whereas an incidence of 3.4 percent hypersensitivity was seen in 414 patients using this type of a preparation for longer than 10 years (Ref. 8).

In infants and small children, nasal ointment or drops containing menthol may cause spasm of the glottis and cases of dangerous asphyxiation have been reported in infants following local application of menthol. For this reason a warning against the topical application of menthol-containing products directly to the nostrils of infants has been recommended (Refs. 4 and 9). A study of infants and children with respiratory infection who received an ointment containing a mixture of volatile oils including 2.8 percent menthol applied to the chest and neck demonstrated no adverse effect from the inhaled vapors by that route of administration on the rate of clearing of laryngeal inflammation. In this study 35 children, 23 under 2 years of age, with respiratory infection received only standard forms of therapy, e.g., antibiotics and fluids, while 37 children, 30 under 2 years of age, received standard therapy plus the mentholated ointment applied to the chest and neck. Laryngoscopic examination revealed comparable rates of clearing of laryngeal inflammation (Ref. 10).

A liquid mixture of volatile substances including 3.66 percent menthol is placed in the water of a hot steam vaporizer and administered via inhalation. A number of studies involving nearly 900 subjects in which this mixture was administered at recommended doses was not associated with significant complaints of subjectively perceived adverse effects (Refs. 11 through 23). Exaggerated-use studies in adults and children, i.e., exposure for several hours to higher than recommended exposure concentrations either due to sitting in closer proximity to the vaporizer or placing 2 to 5 times the recommended dose of the volatile substance in the vaporizer was not associated with irritating or toxic effects (Refs. 24 and 25).

In two studies, 40 healthy subjects asked to dissolve two candy-base lozenges, each lozenge containing 1.36 mg of menthol together with other volatile oils, every 20 minutes for 2 hours exhibited no adverse effects with the exception of one report of nausea and vomiting. This was attributed to a dislike for the wild cherry flavor of the lozenge (Refs. 26 and 27). In a group of 70 healthy subjects, 50 adults and 20 children ages 8 to 12, half dissolved a menthol-eucalyptus lozenge containing

9.62 mg menthol and 5.55 mg eucalyptus oil every 4 to 8 hours on 2 successive days, the other half dissolved the cough drop base without the aromatics. In this intensive dosage schedule, a slightly larger number of subjects demonstrated mild irritation of the oral mucosa on day 1 and day 2, but there were no differences between the two groups in the severity of irritation or residual findings after day 2. No systemic complaints were reported (Ref. 28). A similar study using a lozenge formulation containing menthol 8.14 mg and eucalyptus oil 4.625 mg versus a lozenge base without volatile substances produced comparable results (Ref. 29).

An aerosolized dosage form of volatile substances including 1 percent menthol has also been utilized for treatment of nasal congestion and cough symptoms. Rats exposed to acute overdoses of the spray in a confined chamber for 6 hours revealed no untoward behaviorial responses or airway tissues abnormality upon autopsy examination (Ref. 30). A group of four monkeys were exposed to 200 gm per day of the aerosol, i.e., 2 gm of menthol total dose in divided doses over an 8-hour period for 14 consecutive days in a confined chamber. Eye irritation was the only pharmacotoxic sign observed during the study (Ref. 31). In humans, such aerosol sprays have been generally safe when used as-directed, but there have been reports of deaths from deliberate sniffing abuse, particularly when the subject inhales from a plastic bag into which the material has been sprayed (Ref. 32). Furthermore, one commercial preparation containing a particular solvent, 1,1,1-trichloroethane, was recently recalled from the market due to potential hazards of this substance (Ref. 33).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of menthol/peppermint oil (topical/inhalant) as an expectorant. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

The local anesthetic effect of menthol vapor has been the justification for including menthol in topically administered ointments and lozenges for alleviation of cough. In a crossover study involving 16 subjects the effects of a 2.8 percent mentholated petrolatum ointment applied to the chest of the subjects was compared to an ointment containing several volatile substances including 2.8 percent menthol, and to petrolatum in suppressing a citric acid aerosol-induced cough. A combination ointment containing menthol induced a significant decrease in cough counts at all challenge times from ½ hour through 2 hours, averaging about 20 percent decrease at the ½ and 1 hour intervals, whereas the single ingredient menthol ointment yielded a significant decrease in cough counts just at the ½ and 1 hour intervals, averaging about 10 percent reduction. The petrolatum yielded no significant decrease in cough counts compared with base line (Ref. 34). Similar results with the combination ointment containing 2.8 percent menthol were obtained in two additional induced-cough studies conducted by the same investigator (Refs. 34 and 35).

A single-blind crossover cough-counting study of 27 patients exhibiting stabilized chronic cough utilized twice daily chest applications of either the ointment containing several volatile substances including 2.8 percent menthol, an ointment containing 1.3 percent eucalyptus oil, or petrolatum base. Neither the ointment mixture nor the eucalyptus oil ointment induced a significant decrease in cough counts compared to placebo after the morning application, but a significant 20 percent cough-count reduction compared to placebo was obtained following the afternoon dose of the ointment mixture. An average reduction in cough counts of about 10 percent compared to placebo was noted following the afternoon dose of eucalyptus oil ointment, but this was not statistically significant (Ref. 36).

A liquid mixture of volatile substances added to the water of a hot steam vaporizer and administered via inhalation contained menthol 3.66 percent, camphor 7 percent, eucalyptus oil 1.7 percent, and tincture of benzoin 5 percent. Three crossover studies compared the effects of this volatile substance containing liquid in steam, 1 tablespoonful per quart of water, to steam alone in suppressing coughs artifically induced by the citric acid aerosol technique. In each case both steam and medicated steam induced a statistically significant reduction in cough counts during the period of administration. In two of the studies the cough reduction with the medicated steam was statistically greater than with steam alone and persisted beyond the period of actual administration to the subject (Refs. 37, 38, and 39). Subjective evaluation studies of adults and infants having cough associated with respiratory infection demonstrated statistically significant antitussive effectiveness of the volatile substances in steam, 1 tablespoon per quart of water, and of steam alone. In some of these studies the effect of the medicated steam was judged statistically superior to the steam alone (Refs. 40, 41, and 42).

The variety of lozenge preparations containing a mixture of volatile substances including menthol have been studied for their ability to suppress citric acid aerosol induced cough in normal subjects. Since each of these lozenge preparations contain different concentrations of menthol and other volatile substances, the results of the study will be individually summarized. The general study format involved an unblinded crossover design in which a group of cough-standardized normal subjects were tested with each of two lozenge formulations, the active formulation and its vehicle control, against cough artificially induced by the citric acid aerosol technique. Two studies involved lozenges in which menthol was the principal active ingredient and consequently represent an indication of the effectiveness of this mode of administering menthol to suppress cough. One of the studies involving 16 subjects used a lozenge containing menthol 2.64 mg and peppermint oil 2.29 mg plus benzyl alcohol 5.76 mg. The active formulation produced significant cough reductions at the 10- to 40-minute challenge periods, reaching a peak of 30 to 35 percent at the 10- and 20-minute intervals whereas the control lozenge produced a significant reduction of 15 to 20 percent at the 10- and 20-minute intervals only (Ref. 43). The other study of ten subjects utilizing a lozenge containing menthol 1.13 mg plus citric acid flavoring produced greater cough reduction than the control lozenge at the 10- through 30-minute challenge periods although both the active and control lozenges in this study produced cough reductions at these time intervals (Ref. 44).

Two studies involving a total of 40 subjects used similar active formulations consisting of menthol 9.6 mg and eucalyptus oil 5.5 mg per lozenge. In these studies the active formulation produced significant cough reductions at the 10- to 40-minute challenge periods, reaching a peak of 25 to 35 percent reduction at the 10- and 20-minute intervals whereas the control lozenge produced a significant reduction of 10 to 15 percent maximum at only the 10-minute challenge (Refs. 45 and 46). In a study of nine subjects receiving lozenge doses of menthol 1.5 mg and eucalyptol 0.35 mg, elevated citric acid thresholds of 120 to 146 percent of control for 3 to 5 hours after dosing were obtained, although a placebo control lozenge was not utilized in this study for comparison (Ref. 47). Another study of 20 subjects utilizing a formulation of menthol 2.78 mg, eucalyptus oil 0.77 mg plus smaller amounts of camphor, thymol, and tolu balsam, produced significant cough reductions at the 10- through 40-minute challenge periods, reaching a peak of 35 percent reduction at the 10- and 20-minute intervals whereas a control lozenge produced a significant reduction of 11 to 17 percent maximum at the 10- and 20-minute challenge periods only (Ref. 48). Similar results were obtained in 16 subjects using an active formulation containing menthol, eucalyptus oil, camphor, thymol, and tolu balsam present in about ½ the amounts utilized in the preceding study (Ref. 49).

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 2.8 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 3.66 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl, or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 1.0 to 12 mg: Allow lozenge to dissolve

slowly in mouth. May be repeated every ½ to 1 hour.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

(iii) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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i. *Pine tar preparations (extract white pine compound, pine tar, syrup of pine tar, compound white pine syrup, white pine).* The Panel concludes that pine tar preparations are safe in the dosage range used as expectorants but effectiveness at those dosages has not been established.

(1) *Safety.* Clinical experience has confirmed that the pine tar preparations are safe in the dosage ranges used as expectorants. The above preparations are administered orally for an expectorant activity. The active ingredient is pine tar, a product obtained by the destructive distillation of wood of various species of pine, usually "Pinus palustrus." It is a viscid blackish-brown noncrystalline

liquid. It has a turpentine-like odor and a sharp taste of organic decomposition. It has been used mainly for diseases of the skin, being slightly irritating, antiseptic, and with local anesthetic properties.

The Panel is unaware of any studies to evaluate the safety of pine tar. It is probably safe in the recommended doses since it has been used for decades without any recorded reports of adverse effects (Refs. 1 through 4).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of pine tar preparations as expectorants. The use of pine tar preparations as expectorants appears to be based solely on tradition. There is no evidence that they are effective as an expectorant when taken orally.

(3) *Proposed dosage.* Adult oral dosage is 1.6 mg every 3 to 4 hours. Children 6 to under 12 years oral dosage is 0.8 to 1.0 mg every 3 to 4 hours. Children 2 to under 6 years oral dosage is 0.4 to 0.5 mg every 3 to 4 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness as an expectorant will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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j. *Potassium guaiacolsulfonate.* The Panel concludes that potassium guaiacolsulfonate is safe in the dosage ranges used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that potassium guaiacolsulfonate is safe in the dosage ranges used as an expectorant. There is no evidence of toxicity in the available literature. Information is sparse, and there is no documentation of adverse reactions.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of potassium guaiacolsulfonate as an expectorant. While subjective studies would indicate that it is ineffective as an expectorant (Refs. 1 and 2), potassium guaiacolsulfonate has been used empirically, for many decades, in expectorant mixtures. Connell, et al. (Ref. 3) showed no change in water content of the respiratory tract of rats. Two papers cited that potassium guaiacolsulfonate is not metabolized to guaiacol (Refs. 1 and 2).

Many of the submissions to the Panel listed preparations containing potassium guaiacolsulfonate at 80 to 90 mg/5 ml with 1 tablespoonful recommended as the adult dose (240 to 270 mg per dose). One study, however, employed an adult dose of 500 mg (Ref. 4). Based on the scanty evidence, the Panel concludes that there is a wide dose range with no specific optimum level for expectorant activity.

(3) *Proposed dosage.* The Panel is unable to determine a proposed dosage. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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k. *Sodium citrate.* The Panel concludes that sodium citrate is safe in the dosage range used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience over more than a half a century has confirmed that sodium citrate is safe in the dose ranges used as an expectorant. It is mildly diuretic and, in larger doses, may be laxative. Gastric irritation can be produced if taken undiluted (Ref. 1).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of sodium citrate as an expectorant. Goodman and Gilman (Ref. 1) states that the use of citrates as expectorants is mainly empirical and it is "probable that the water ingested with them is the basis for any beneficial effect." A similar preparation, potassium citrate was found to have very little effect upon the output of respiratory tract fluid in a dose as high as 0.4 gm/kg of body weight (Ref. 2).

(3) *Proposed dosage.* Adult oral dosage is 1.0 to 2.0 gm every 2 to 4 hours taken well diluted with at least ½ glass of water or fruit juice (Ref. 3). Children 6 to under 12 years oral dosage is 0.5 to 1.0 gm every 2 to 4 hours diluted as above with water or fruit juice. Children 2 to under 6 years oral dosage is 250 to 500 mg every 2 to 4 hours diluted as above with water or fruit juice. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warnings:* (i) "*Caution:* This product must be taken with adequate amounts of fluids (½ to 1 glass) with each dose".

(ii) "*Caution:* Do not take this product if you have heart trouble or kidney disease except under the advice and supervision of a physician".

At smaller amounts, less than the proposed doses above, sodium citrate has been employed in liquid mixtures for its mild saline taste. In these instances, it is not classified as an active ingredient, and no labeling claim should be made for it since it is being used as a flavoring agent.

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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(2) Boyd, E. M., B. Palmer and B. Pearson, "Is There Any Advantage in Combining Several Expectorant Drugs in a Compound Cough Mixture?" *Canadian Medical Association Journal*, 54:216–220, 1946.

(3) *Remington's Practice of Pharmacy*, 12th Ed., Edited by Martin, E. W., p. 814, 1961.

l. *Terpin hydrate preparations (terpin hydrate, terpin hydrate elixir).* The Panel concludes that terpin hydrate is safe in the dosage ranges used as an expectorant but there are insufficient data to permit final classfication of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that terpin hydrate is safe in the dosage ranges used as an expectorant.

A few papers noted gastrointestinal distress from dosages of 340 to 680 mg/24 hours, with nausea and vomiting (Refs. 1 and 2). Elixir terpin hydrate has a high alcoholic content of approximately 42 percent which could be subject to alcohol abuse (Ref. 3). The Panel has recognized the potential for such abuse as stated in a previous section of this document. (See part II. paragraph G. above—Drug Misuse and Abuse.) Based on the available data and its long history of use, the Panel concludes that terpin hydrate is safe for OTC use in the dosages discussed below. However, because of the high alcohol content required to formulate and manufacture elixir terpin hydrate, the Panel recommends that elixir terpin hydrate not be used in children younger than 12 years.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of terpin hydrate as an expectorant. The majority of papers in the literature question the effectiveness of terpin hydrate and indicate that it is probably harmless and useless (Refs. 2 through 5). Two papers indicate that at a dose of 300 mg 4 times daily, it had a "loosening effect," but these were subjective evaluations (Refs. 6 and 7). The Panel concludes that the information available is not sufficient to determine that terpin hydrate is effective as an expectorant.

(3) *Proposed dosage.* Adult oral dosage is 200 mg every 4 hours not to exceed 1200 mg in 24 hours. The elixir should not be given to children under 12 years of age but terpin hydrate by itself or in a nonalcoholic mixture can be used. Children 6 to under 12 years oral dosage is 100 mg every 4 hours not to exceed 600 mg in 24 hours. Children 2 to under 6 years oral dosage is 50 mg every 4 hours not to exceed 300 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warnings.* (i) "May produce nausea and vomiting".

(ii) For elixir products containing 42 percent alcohol: *"Caution:* This product contains 42 percent alcohol and should not be given to children under 12 years except under the advice and supervision of a physician".

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

REFERENCES

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(2) Hirsch, S. R., "The Use of Expectorants," *Wisconsin Medical Journal,* 70:153–156, 1971.

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(4) Richerson, H. B., "Expectorants," *Journal of the Iowa Medical Society,* 58:875–876, 1968.

(5) Grzybowski, S., "Cough Medicines," *Canadian Medical Association Journal,* 92: 619–620, 1965.

(6) Rose, J., "The Ineffectiveness of Expectorants," *Canadian Medical Association Journal,* 69:494–495, 1953.

(7) Boyd, E. M., "Expectorants and Respiratory Tract Fluid," *Pharmacological Reviews,* 6:521–542, 1954.

m. *Tolu preparations (tolu, tolu balsam, tolu balsam tincture).* The Panel concludes that tolu balsam is safe in the dosage range used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that tolu preparations are safe in the dosage ranges used as expectorants. Tolu balsam can be considered safe in the dosages used for expectorant activity when administered orally or by inhalation.

There is no documentation as to toxicity at the dose levels in general usage in man. One report (Ref. 1) states that huge doses, "1,000 times that recommended," when given by inhalation produced an acute inflammation of the tracheal lining in rabbits.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of tolu preparations as expectorants. There is no evidence that tolu balsam possesses expectorant activity.

Several reports by Boyd and his coworkers (Refs. 2 through 4) are conflicting and consist for the most part of statements rather than data from studies, i.e., "Syrup of Tolu did have an expectorant action." Certain volatile oils (Friar's balsam) stimulate the output of respiratory tract fluids (RTF) or bronchial secretions (Ref. 3). In another paper (Ref. 4), the author states that inhalation by animals of therapeutic doses of certain volatile oils (Friar's balsam) has no effect upon respiratory tract fluids. A standard text states that tolu balsam syrup is "widely employed as a vehicle for expectorant drugs but has no specific virtue for this purpose" (Ref. 5). The Panel takes cognizance of the fact that tolu balsam has been used for many decades as an ingredient in steam inhalations and in oral expectorant mixtures but concludes that there are insufficient data to determine the effectiveness of tolu balsam as an expectorant.

(3) *Proposed dosage.* Adult oral dosage is 50 mg every 2 to 3 hours. Children 6 to under 12 years oral dosage is 25 mg every 2 to 3 hours. Children 2 to under 6 years oral dosage is 12.5 mg every 2 to 3 hours. For children under 2 years, there is no recommended dose except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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n. *Turpentine oil (spirits of turpentine) (topical/inhalant).* The Panel concludes that turpentine oil is safe in the dose ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that turpentine oil is safe when applied topically or used as an inhalant in the dose ranges used as an expectorant. The Panel concludes that oil of turpentine is safe when applied externally or vaporized in boiling water as a steam inhalant. However, the Panel has determined elsewhere in this document that it is not safe for OTC use when used orally as an expectorant. (See part IV. paragraph B.2.f. above—Turpentine oil (spirits of turpentine) (oral).)

Oil of turpentine is a volatile oil consisting of a mixture of pinenes derived from the oleoresin obtained from Pinus palustrus. Nelson et al. (Ref. 1) found exposure to a vapor of 420 to 560 mcg/l acceptable to most of their human subjects. The threshold for industrial exposure for 8 hours has been set at 560 mcg/l. The maximum concentration obtainable with a currently marketed OTC preparation is 36 mcg/l (Refs. 2 and 3). No histological evidence of pulmonary lesions were seen in mice and rats exposed to lethal concentrations of turpentine vapors (Ref. 4). Inhalation of 300 mcg/l of turpentine vapor by mice for 15 minutes did not influence the electrocardiogram, respiratory minute volume, pulmonary airway, resistance or compliance (Ref. 5). One study in mice using a mixture of volatile oils, one of which was turpentine, showed a decrease in pulmonary antibacterial activity (Ref. 6). Two other studies showed no change when the mixture was used (Refs. 7 and 8).

In several studies in children and infants suffering from minor breathing discomforts associated with the "common cold," no side effects that were drug related were observed when a medicated steam was administered (Refs. 9 through 13). Turpentine has been widely used as a part of a mixture of volatile oils for many years, with approximately two complaints per million packages purchased (Ref. 14).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of turpentine oil as an expectorant when applied externally or vaporized in boiling water as a steam inhalant due to a lack of objective measurement studies of the substance by itself.

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 4.0 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help

the vapor rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use a 5.5 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl, or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required from only one additional well-controlled cough-counting objective study in patients with coughs due to respiratory disease in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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(14) OTC Volume 040279.

Category III Labeling

The Panel concludes that substantiation by additional data is required before statements regarding duration of action, e.g., "all day", "all night", "for hours" will be acceptable. Such statements must specify in the labeling the number of hours of relief claimed. The statements must be verified by appropriate documentation.

C. DATA REQUIRED FOR EVALUATION

The Panel has agreed that the protocols recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. *Principles in the design of an experimental protocol for testing expectorant drugs.* a. *General principles.* The effectiveness of an expectorant preparation is based on its ability to facilitate the removal of sputum from the respiratory passageways and thus clear the airway of retained secretions. By aiding in the removal of these secretions and through a soothing effect on irritated mucous membranes, it will indirectly ease the act of coughing. While the ease in raising secretions may seem simple to measure and assess, there are, at present, no suitable objective methods for evaluating this. This difficulty stems, in part, from a lack of basic knowledge concerning the biochemical and physiochemical nature of respiratory tract secretion in various respiratory diseases, as well as the changes produced by expectorant drugs, and the lack of evidence as to which property of sputum correlates best with ease of expectoration. Because of this, the subjective evaluation of the patient must be relied upon the assessment of the drug's expectorant activity.

b. Selection of patients. Based upon the method of study to be used, two types of patients may be selected. One patient type who would be chosen for a crossover study could include subjects with chronic cough due to chronic pulmonary disease such as chronic bronchitis, pulmonary emphysema, inactive pulmonary tuberculosis, etc., and whose condition is relatively stable with no evidence of intercurrent infection that would affect cough or character of the sputum. A second patient type could include subjects with an acute upper respiratory infection, such as an acute bronchitis or tracheobronchitis, in which a dry nonproductive cough is a prominent feature. Because the production of respiratory secretions may be influenced by other systems, such as the circulation, patients with congestive heart failure or significant renal or hepatic disease must be excluded. Furthermore, every effort must be made to maintain the same relative state of hydration and activity, and drugs must be prohibited that may affect sputum, such as the anticholinergics and antihistamines. While nonsmokers would be preferable as subjects, the smoking habits of patients must be carefully documented and maintained at the same level throughout the clinical trials. No smoking would be permitted during the actual recording sessions. While impractical to control, the effect of environmental factors such as temperature, humidity, and degree of air pollution should be recognized.

c. *Methods of study* (1) *Double-blind crossover design in patients with chronic lung disease.* A suitable period for baseline studies must be performed prior to the administration of the test drugs. During this period, the following subjective indices will be noted: Ease of expectoration; character of the cough (whether productive or not); frequency of coughing; and breathing comfort, i.e., heavy, noisy, rattling, etc. Additional help in evaluating effectiveness may be provided by some objective indices such as: The volume and dry weight of sputum collections over a given time (12 to 24 hours); the character and color of the sputum raised; and some measure of its flow properties, such as viscosity or consistency. If a cough suppression claim is to be substantiated, an objective cough-counting study must be done as discussed under antitussives. (See part III. paragraph C. above—Data Required for Evaluation.) Following baseline studies, similar observations are obtained during the administration of the drug and placebo which must be indistinguishable from each other, randomized, and provided at a dose and time sequence recommended for OTC use. This type of study would require approximately 3 weeks, 1 week on each preparation and 1 week for the baseline data.

(2) *A randomized double-blind design in patients with acute upper respiratory infections.* Groups of patients would receive either a placebo or the drug under study in a similar dose and time interval as recommended for OTC use over a period of 3 to 5 days. Similar observations, as discussed above, would be obtained where possible to evaluate effectiveness, but no prior baseline period would be obtainable with this model and most of the data would be limited to the subjective indices. Patient diaries would be kept in which the type of symptoms, their duration and severity as well as adverse reactions would be recorded daily.

d. *Interpretation of data.* Evidence of drug effectiveness is required from a minimum of three positive studies based on the results of three different investigators or laboratories. At least one of the three studies must be in patients with chronic pulmonary disease. Approximately 20 to 30 patients will be required for the crossover study described above. Because of the marked variability in cough and sputum production in acute respiratory disease from day to day together with the spontaneous waning of

symptoms as part of its natural history, a much larger number of patients, possible 75 or more, must be studied for this group. The subjective indices to be evaluated can be scored for statistical analysis, with a p value of 0.05 or less (95 percent confidence level) being acceptable as evidence of a drug effect when compared with placebo.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

e. *Evaluation of safety.* Tests for safety of expectorant ingredients not reviewed by this Panel should involve the usual animal studies and observations in man relevant to various organs and system, i.e., cardiovascular, respiratory, renal, hepatic, cerebral, and hematologic. Of special note insofar as expectorant drugs may be concerned are such factors as carcinogenicity, effect on clotting mechanisms, thyroid function, electrolyte and acid-base balance, in addition to the general areas mentioned above.

V. Bronchodilators

A. General Discussion

Bronchodilators are agents used for the symptomatic treatment of the wheezing and shortness of breath associated with asthma. These agents are used to overcome the spasm that causes narrowing of the bronchial air tubes. These drugs are also used but are much less effective in relieving the shortness of breath of chronic bronchitis and emphysema. The drugs most commonly used as bronchodilators are some sympathomimetics (sympathomimetic amines), theophylline, and theophylline salts. The Panel has classified these two major forms of bronchodilators, i.e., sympathomimetic amines and theophyllines, as distinct pharmacologic groups. The sympathomimetic amines and theophyllines work well when given together, but it is preferable that the dose of each should be individualized for each patient (Ref. 1).

The sympathomimetics may be given orally (ephedrine and methoxyphenamine), by aerosol inhalation (epinephrine solution), by rectal installation, by injections under the skin or into the muscle of the upper arm or buttocks, and in some situations under medical supervision sympathomimetics may be used under the tongue.

Theophyllines are usually given by oral administration but they may also be given, under medical supervision, by the rectal route or by intravenous injection. The oral preparations of theophylline are not affected by food in the stomach (Ref. 2). Excessive doses result in high blood levels which cause nausea and vomiting. Individuals metabolize these drugs at different rates. Therefore, some patients require only a relatively small dose of the drug while others require quite large doses for a satisfactory effect. Occurrence of nausea or vomiting will indicate when the dose of drug is excessive. Only one of the theophyllines and only one route of administration should be used at a time because of the additive effects of these drugs.

Adverse reactions associated with the sympathomimetic bronchodilators consist primarily of those affecting the cardiovascular and central nervous systems. These drugs may cause arrhythmias, hypertension, dizziness, tremor, nervousness, and sleeplessness. They may also cause a rise in blood sugar concentration and in older men they may cause slowing or even obstruction to the urinary stream. Because of these possible reactions, the drugs should be used with caution in individuals with cardiac disease, hypertension, hyperthyroidism, diabetes, or prostatic enlargement.

The theophyllines given orally or rectally may produce nausea and vomiting which, in extreme cases, may result in dehydration and shock.

Theoretically a combination product containing a theophylline drug and a sympathomimetic to be taken by mouth, for example, as a tablet, should be very effective and convenient. However, to obtain the most effective bronchodilation, the dose of theophylline should be individualized because of individual variation in the metabolic breakdown of theophyllines (Ref. 3).

The Panel is concerned that in a patient who is a rapid metabolizer of theophylline, a fixed-dose of a theophylline and a sympathomimetic in an oral combination product might have reduced effectiveness because of a low theophylline dose. If the number of dosage units, e.g., combination tablets taken, is increased to provide an effective theophylline dose, the dose of sympathomimetic might be excessive and cause side effects. Conversely, in a patient who is a slow metabolizer of theophylline, the standard dose of an oral combination product of theophylline and a sympathomimetic might produce theophylline toxic effects. If the number of combination tablets is decreased to avoid these side effects, then the dose of sympathomimetic might be so low as to have a low effectiveness.

Therefore, it would appear that single ingredient preparations containing either a theophylline or a sympathomimetic would be both more effective and have increased safety as compared to combination products.

Although the bronchodilators are generally safe for OTC use at recommended dosage and are effective in relieving the shortness of breath caused by bronchospasm, the Panel emphasizes that these preparations should not be used unless a diagnosis of asthma has been made by a physician and a dosage schedule of OTC medicine has been established by a physician.

Patients with asthma may also require prescription drugs which may have serious dangers and side effects and there is, then, an added need for continued medical supervision.

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B. Categorization of Data

1. *Category I conditions under which bronchodilator ingredients are generally recognized as safe and effective and are not misbranded.*

Category I Active Ingredients

The Panel has classified the following bronchodilator active ingredients as generally recognized as safe and effective and are not misbranded:

Sympathomimetic amines

Ephedrine preparations: Ephedrine, Ephedrine hydrochloride, Ephedrine sulfate, Racephedrine hydrochloride

Epinephrine preparations (inhalant): Epinephrine, Epinephrine bitartrate, Epinephrine hydrochloride (racemic)

Methoxyphenamine hydrochloride

Theophyllines

Theophylline preparations: Aminophylline, Theophylline anhydrous, Theophylline calcium salicylate, Theophylline sodium glycinate

a. *Ephedrine preparations (ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine, hydrochloride).* The Panel concludes that ephedrine preparations are safe and effective for OTC use as bronchodilators as specified in the dosage section discussed below.

(1) *Safety.* Ephedrine, when absorbed systemically, has effects both on the brain (central) and on nerve endings (peripheral) (Ref. 1). In clinical usage, the central effects are stimulatory and include tenseness, nervousness, tremor and sleeplessness. Peripheral effects include bronchodilatation, and possibly shrinkage of mucous membranes (decongestion), although this has not been documented. Other peripheral effects include awarness of heartbeat and rapid heart beat accompanied usually by some elevation of blood pressure. However, a study by Dulfano and Glass on 26 asthmatics between the ages of 28 and 61 years showed that a single dose of 25 mg had no significant effect on either heart rate or blood pressure (Ref. 2). Another recent study of the cardiovascular effects of 25 mg ephedrine in 20 asthmatics showed there was only a modest increase in heart rate up to 11 beats per minute as a maximum, and the systolic and diastolic blood pressure showed no significant change (Ref. 3). In spite of these findings, the cardiovascular and central effects appear to set limits on dosage, limits which vary widely among patients as judged by clinical experience. Loss of appetite and nausea also occur in some patients. Difficulty in urination may occur in older males who might have enlarged prostate glands. The drug, under these circumstances, exacerbates obstruction to urine flow by causing spasm of the outlet of the bladder. Overdosage results in exaggeration of the side effects which patients describe as disagreeable and can usually be depended upon to prevent overuse or abuse. Ordinary doses may cause marked and potentially dangerous increases in blood pres-

sure in patients taking drugs containing monoamine oxidase (MAO) inhibitors.

(2) *Effectiveness.* The bronchodilator effects of ephedrine taken by mouth are slow in onset, probably 15 to 25 minutes, and probably persist for 2 to 3 hours, based on the Panel's clinical observations. The drug is less effective as a bronchodilator than epinephrine, and its usefulness is limited to the milder forms of asthma.

A dose of 25 mg by mouth given to asthmatic patients prevented the bronchospasm induced by various chemicals (Ref. 4). The fall in vital capacity induced by histamine was prevented to the extent of 40 percent and that by methacholine to the extent of 32 percent (Ref. 4). Although based on objective measurements, this study does not seem to have been rigorously planned or executed as judged by today's standards.

In a double-blind comparison of 24 mg ephedrine and a combination of 24 mg ephedrine and 130 mg theophylline, measurements including specific airway resistance, vital capacity, and FEV_1 (forced expiratory volume in one second—a measurement related to airway obstruction, the higher the figure the better the airflow and the less the obstruction in the air tubes) showed that ephedrine significantly decreased the first and increased the last two over a period of 2 hours, an effect that was enhanced and prolonged by the presence of theophylline (Ref. 5). Each preparation also contained 8 mg of phenobarbital. Although a placebo was not included, these findings carried out with sophisticated objective measurements, strongly support a bronchodilator effect for ephedrine.

In a study comparing ephedrine and terbutaline in 26 asthmatics, it was shown that 25 mg ephedrine resulted in a maximal change of FVC 11 percent, FEV_1 18 percent, MVV 17 percent, MMF 25 percent, and MEFR 24 percent over the controlled figures. The improvement in the pulmonary function tests were statistically significant between 120 and 240 minutes after taking a single dose. The results were similar to 2.5 mg terbutaline but were less than the effect of 5.0 mg terbutaline (Ref. 2).

In a recent study of 20 patients with asthma, 25 mg ephedrine showed effective bronchodilation for up to 4 hours (the respiratory function tests of FVC, FEV_1 and airway resistance were used) (Ref. 3).

(3) *Dosage.* Adult oral dosage is 12.5 to 25 mg not more often than every 4 hours not to exceed 150 mg in 24 hours. Children 2 to under 12 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician. There is insufficient information as to the possible toxic effect of ephedrine in this age group.

The Panel strongly recommends that ephedrine be available as scored tablets containing 12.5 mg and 25 mg ephedrine per tablet to permit flexibility in dosage.

(4) *Labeling.* The Panel recommends the Category I labeling for bronchodilator active ingredients. (See part V. paragraph B.1. below—Category I Labeling.) In addition the Panel recommends the following specific labeling: *Warnings.* (i) *"Caution:* Do not continue to take this product but seek medical assistance immediately if symptoms are not relieved within 1 hour or become worse".

(ii) "Nervousness, tremor, sleeplessness, nausea and loss of appetite may occur".

(iii) "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland".

(iv) *Drug Interaction Precaution.* "Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor".

(v) "Do not give this product to children under 12 years except under the advice and supervision of a physician".

(vi) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 6 to under 12 years oral dosage is 6.25 to 12.5 mg not more often than every 4 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is 0.3 to 0.5 mg/kg of body weight not more often than every 4 hours not to exceed 2 mg/kg of body weight in 24 hours.

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b. *Epinephrine preparations (epinephrine, epinephrine bitartrate, epinephrine hydrochloride (racemic)) (inhalant).* The Panel concludes that epinephrine is safe and effective for OTC use as a bronchodilator as specified in the dosage section discussed below.

(1) *Safety.* Wide use of epinephrine aerosols for temporary relief of spasm that causes narrowing of air tubes has been attended by few and mild side effects. However, one early report by Benson and Perlman (Ref. 1) raised the possibility that excessive use of epinephrine aerosols caused serious harm to the lining of the air tubes, resulting in an increase in air tube secretions which in turn predisposes to infection and collapse of small areas of the lungs. Alternative causes for these changes were not seriously considered. The report was retrospective and it found that a greater number of deaths occurred in users of epinephrine aerosols, 48 of 618 (7.4 percent) as compared with 22 of 1,588 nonusers (1.4 percent). The possibility that the users might have had a more severe illness than nonusers was not considered and might well explain the findings.

In a study of 86 patients with various types of cardiac involvement and 16 patients with uncontrolled diabetes who inhaled aqueous epinephrine from a nebulizer (Ref. 2), no untoward effects developed following administration of many times the dose considered to be effective in asthma, nor were there significant changes in pulse rate, blood pressure, electrocardiogram, or blood sugar level. The authors conclude that the presence of cardiovascular disease or diabetes is not a contraindication to the use of d,l-epinephrine (racemic) or l-epinephrine (levorotatory) by inhalation.

Epinephrine aerosol was used for many years before its safety was seriously questioned. The question arose because of an increase in the number of deaths among those using a chemically related drug, isoproterenol, a prescription drug, which also caused aggravation of the airway obstruction in some patients.

The reports of an increase in deaths from isoproterenol had their origin in England (Ref. 3). A possible explanation was that the preparation used there had a concentration of isoproterenol 5 times greater than that used in Sweden, Australia, and the United States, where no such increase in deaths had been noted (Ref. 4). It was inferred that the high concentration of isoproterenol accounted for the increased deaths. Deaths decreased when a lower concentration of isoproterenol was used.

Aggravation of the obstructive abnormality clearly occurs in some patients with asthma following administration of isoproterenol (Ref. 5). This may be due to some fraction of absorbed isoproterenol being converted to a metabolite which could predispose to causing spasm of air tubes (Ref. 6).

It has been further observed (Ref. 7) that isoproterenol by inhalation, while producing bronchodilation, may simultaneously cause a small and usually clinically insignificant fall in blood oxygen level. That this has not been observed with epinephrine by inhalation may merely reflect the small amount of interest in this drug in the years since techniques for making the necessary measurements have become readily available, but the tests have not been done.

It is unlikely that these observations of toxicity concerning isoproterenol are relevant in judging the safety of epinephrine by inhalation. Epinephrine stimulates both alpha and beta receptors (Ref. 8) and would be expected to have a local constrictor effect on blood vessels in the lungs as it does in subcutaneous tissue, an effect expected to limit systemic absorption of the administered

drug. Isoproterenol is predominantly a stimulator of beta receptors (Ref. 8) and would be expected to cause vascular dilatation and systemic absorption of the administered drug. The relative therapeutic advantage or disadvantage of this difference between the two drugs is unknown and needs further study.

Since the isoproterenol adverse reactions are not known to bear on the safety of epinephrine by inhalation and since these postulated hazards would appear to be avoidable by using low concentrations and by instructing the patient by appropriate labeling, epinephrine by inhalation is judged by the Panel to be a safe preparation for OTC use.

One additional difficulty may arise which applies to all sympathomimetic drugs self-administered by inhalation for relief of asthma. A patient with severe and worsening obstructive pulmonary disease may obtain very temporary relief and this relief may give a false sense of security. Under such circumstances the patient may postpone calling a physician or going to a hospital until his disease has reached life-threatening severity and the suggested labeling in this document takes this possibility into account. The safety of propellants used in these preparations has not been reviewed by this Panel because they are considered to be pharmaceutical necessities which should be reviewed independently by the Food and Drug Administration. The side effects of sympathomimetics are worsened by monoamine oxidase inhibitors which prevent the breakdown of these drugs.

(2) *Effectiveness.* A number of letters from experts in the field of respiratory and allergic disease attest to the safety and effectiveness of inhaled aerosolized epinephrine (Ref. 9). In a double-blind study in asthmatics the timed vital capacity ($FEV_{0.5}$) was compared after metered inhalations of 0.125 mg epinephrine delivered per inhalation, 0.06 mg isoproterenol delivered per inhalation and a placebo (Ref. 10). The means taken to maintain experimental control are not described. Both epinephrine and isoproterenol gave significant increase within 15 minutes accompanied by symptomatic relief whereas the placebo gave little change. Side effects were not mentioned.

In a comparative study of several bronchodilator preparations including epinephrine but lacking a placebo (Ref. 11), epinephrine and the other preparations gave improved bronchial air flow in 12 asthmatic subjects. A specific bronchodilator effect for the preparations given seems highly probable but remains unestablished because of the lack of experimental control and the failure to include a placebo. In an uncontrolled study of the capacity of sympathomimetic drugs to prevent the fall in vital capacity and expiratory flow rate induced by methacholine and histamine (Ref. 12), inhaled epinephrine was effective.

(3) *Dosage.* Adults and children 4 years and above inhalation dosage is 1 to 3 inhalations of a 1 percent aqueous solution of l-epinephrine or the equivalent in a pressurized preparation not more often than every 3 hours, except under the advice and supervision of a physician. For children under 4 years, there is no recommended dosage except under the advice and supervision of a physician.

Children and adolescents should not have unsupervised access to this inhaler. There is the possibility of abuse of this material and possible adverse effects on the heart if excessively used.

(4) *Labeling.* The Panel recommends the Category I labeling for bronchodilator active ingredients. (See part V. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling for preparations of epinephrine used by inhalation: *Warnings.* (i) "Do not take this product at higher than recommended doses except under the advice and supervision of a physician for it may cause nervousness and rapid heart beat".

(ii) *"Caution:* Do not continue to take this product but seek medical assistance immediately if symptoms are not relieved within 20 minutes or become worse".

(iii) "Do not take this product if you have heart disease or high blood pressure except under the advice and supervision of a physician".

(iv) *"Drug Interaction Precaution.* Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor".

(v) "Keep this product out of reach of children and adolescents because unsupervised access may cause abuse or possible adverse effects on the heart if excessively used".

(vi) "Do not give this product to children under 4 years except under the advice and supervision of a physician".

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c. *Methoxyphenamine hydrochloride.* The Panel concludes that methoxyphenamine hydrochloride is safe and effective for OTC use as a bronchodilator as specified in the dosage section discussed below.

(1) *Safety.* In a crossover study in 12 asthmatics, comparing 100 mg methoxyphenamine orally against 30 mg ephedrine sulfate, the types of side effects noted were similar although the frequency of complaints of side effects were only about one-half as frequent with methoxyphenamine. Other studies in asthmatic patients have also reported a lower incidence of side effects, particularly blood pressure changes and central nervous system stimulation, with comparable bronchodilator doses of methoxyphenamine and ephedrine (Refs. 1 through 4). Patients with a history of ephedrine intolerance were often able to tolerate 100 to 200 mg methoxyphenamine without experiencing the usual ephedrine-like side effects of nervousness, insomnia, tremor, and headache (Refs. 2 and 5). The most common side effects of methoxyphenamine appear to be dryness of mouth and mild anorexia (Ref. 4).

(2) *Effectiveness.* In asthmatic patients, oral methoxyphenamine 200 mg and ephedrine sulfate 30 mg offered comparable protection against decreased vital capacity and asthma-like symptoms due to parenterally administered histamine or methacholine (Refs. 1 and 6). Objective measurement studies in asthmatic patients have revealed an increase in vital capacity, up to 20 percent over a 4-hour period, following oral methoxyphenamine 100 to 200 mg (Refs. 2, 4, and 7). Of 61 asthmatic patients who took 100 mg every 4 hours, 37 obtained subjective relief of breathing difficulty. Six of the remaining 24 gained relief with a 200 mg dose every 4 hours (Ref. 2).

No data on the use of methoxyphenamine in children under 12 years are available and there has been little clinical experience with this drug in children. The Panel concludes that methoxyphenamine should not be used in children under 12 years until such time as satisfactory evidence of safety and effectiveness is available.

(3) *Dosage.* Adult oral dosage is 100 mg every 4 to 6 hours not to exceed 600 mg in 24 hours. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for bronchodilator active ingredients. (See part V. paragraph B.1 below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warnings.* (i)

"Caution: Do not continue to take this product but seek medical assistance immediately if symptoms are not relieved within 1 hour or become worse."

(ii) "Nervousness, tremor, sleeplessness, nausea and loss of appetite may occur".

(iii) "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes or difficulty in urination due to enlargement of the prostate gland".

(iv) "*"Drug Interaction Precaution.* Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor".

(v) "Do not give this product to children under 12 years except under the advice and supervision of a physician".

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d. *Theophylline preparations (aminophylline, theophylline anyhydrous, theophylline calcium salicylate, theophylline sodium glycinate).* The Panel concludes that the theophylline preparations are safe and effective for OTC use as bronchodilators as specified in the dosage section discussed below when the dosage is based on the anhydrous theophylline equivalent.

(1) *Safety.* The most commonly encountered adverse effects of theophylline—anorexia, nausea, and vomiting—are apparently centrally mediated. Whether administered orally as uncoated tablets, by injection, or rectally, gastrointestinal symptoms in adults and children are usually negligible if whole blood levels of theophylline do not exceed 8 μg/ml (equivalent to plasma levels of 15 μg/ml). The corresponding plasma level is greater because theophylline does not enter the red blood cells (Refs. 1 through 7). Gastrointestinal symptoms were associated with orally administered aminophylline (theophylline ethlenediamine) when whole blood levels of theophylline exceeded 11 μg/ml (equivalent to plasma levels of 20 μg/ml) (Ref. 1).

Aminophylline administered as an uncoated tablet or theophylline as an alcoholic elixir is quite rapidly and reproducibly absorbed within 1 hour from an empty stomach. Thus, oral absorption and tissue response to a given concentration of theophylline as well as rate of renal excretion are fairly uniform from patient to patient. However, administration with meals or as an enteric coated tablet markedly contributes to slowing and variability in extent of absorption (Refs. 5 and 7). However, recent studies showed that food makes little difference in the absorption of theophylline provided the tablet has a satisfactory dissolution time (Refs. 8 and 9). Studies of theophylline indicate that variations between patients in their maintenance dose requirements are attributable to remarkable differences in the rate at which theophylline is metabolized. In one study of 83 patients, oral aminophylline dosage ranged from 400 to 3,200 mg/24 hours in order to maintain therapeutic blood levels. About 10 percent of patients receiving 300 mg every 4 hours for at least 48 hours experienced loss of appetite, nausea, and vomiting. Despite apparent variations in rate of theophylline metabolism between patients, each individual is internally quite stable in terms of rate of handling this drug so that it is possible to individualize a safe and effective dose for continued therapy (Ref. 1).

In children, oral doses of aminophylline of 4 to 5 mg/kg every 8 hours (80 percent of this dose for theophylline calculated as the free base) is recommended as generally devoid of undesirable side effects (Refs. 8 and 9). Severe toxicity in children may include vomiting with blood in the vomitus and dehydration, central nervous system stimulation leading to convulsions and coma, and cardiovascular collapse. The majority of literature reports of theophylline and aminophylline toxicity in children, and particularly those resulting in death, have been associated with use of aminophylline suppositories. Administered dosage of suppositories in reported toxicity cases ranged from a normal dosage of 10 mg/kg/24 hours to 75 mg/kg/36 hours (Refs. 8 and 10 through 29). Analysis of the cases of toxicity with recommended dosage of suppositories reveal the concurrent oral or parenteral administration of a theophylline preparation. Because of the toxicity potential from overdose unless the dose is individualized to the needs of a child on a mg/kg basis, the Panel believes that such OTC products should not contain labeling with a recommended dosage for children.

Aminophylline, due to its ethylenediamine content, may produce a contact-type dermatitis upon systematic administration to individuals previously sensitized to the topical application of ethylenediamine (Ref. 30).

(2) *Effectiveness.* Following intravenous aminophylline in a variety of patients with narrowing of the air tubes caused by spasm, the degree of objectively measured bronchodilation using measurements of air flow and airway resistance was correlated with whole blood levels of theophylline between 2 μg/ml up to a maximum effect at 8 μg/ml (equivalent to plasma levels of 3.6 to 14.5 μg/ml). A study of airway resistance changes in adult asthmatics following single oral doses of aminophylline demonstrated minimum whole blood levels of theophylline for maximal bronchodilator effect to range from 4.5 to 11 μg/ml (equivalent to plasma levels of 8 to 21 μg/ml). Because of patient variability in metabolism of aminophylline, the authors found that doses of 400 to 3,200 mg/24 hours, averaging 1,200 mg/24 hours, were needed to maintain therapeutically effective "trough" levels (middosing blood levels) of theophylline in the 5.5 to 11 μg/ml range. These authors recommend 300 mg aminophylline (240 mg anhydrous theophylline every 6 hours, 4 times daily (Ref. 1). Following 130 mg doses, blood levels at best reach 4.3 μg/ml (equivalent to plasma levels of 7.6 μg/ml) (Refs. 1, 3, and 31 through 33). Since the blood level attained and maintained in a given patient is dependent on drug metabolism rate, which varies among individuals, an OTC dose recommendation of 100 to 200 mg of anhydrous theophylline equivalent should help patients individualize the dose for optimal response yet minimize side effects.

The Panel recommends that scored compressed tablets in dosage units of 50 mg, 100 mg and 200 mg of anhydrous theophylline equivalent be made available for OTC use. The Panel is concerned that theophylline tablets be readily absorbed when ingested. All tablets must pass a satisfactory dissolution test. The Panel recommends that each tablet formulation be tested according to the procedures described in the United States Pharmacopeia XIX (Ref. 34). The tablets shall be considered satisfactory for OTC use if the quantity of theophylline dissolved within 15 minutes is not less than 50 percent of the labeled amount (based on anhydrous theophylline equivalent content) and the quantity of theophylline dissolved within 30 minutes is not less than 90 percent of the labeled amount of theophylline (based on anhydrous theophylline equivalent content) for any of the tablets tested. The resulting data should be submitted to the Food and Drug Administration prior to marketing.

A double-blind controlled study in 300 asthmatic children, ages 6 to 12, receiving 150 mg theophylline by mouth in plain capsules correlated with significant improvement as measured by pulmonary function tests with theophylline blood levels greater than 3.2 μg/ml (equivalent to plasma levels of 6 μg/ml) (Ref. 3).

A review of oral theophylline drugs lists the anhydrous theophylline equivalents in various proprietary preparations (Ref. 29). For purposes of standardization, the dosage recommendations of the Panel are based on anhydrous theophylline equivalent content.

(3) *Dosage.* Adult oral dosage based on the anhydrous theophylline equivalent is 100 to 200 mg every 6 hours not to exceed 800 mg in 24 hours. Children 2 to under 12 years oral dosage is identified in the labeling section discussed below under professional labeling. For children

under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

The Panel recommends that scored compressed tablets in dosage units of 50 mg, 100 mg and 200 mg of anhydrous theophylline equivalent be made available for OTC use.

(4) *Labeling.* The Panel recommends the Category I labeling for bronchodilator active ingredients. (See part V. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warnings.* (i) "Do not exceed recommended dosage except under the advice and supervision of a physician".

(ii) "Do not take this product if nausea, vomiting or restlessness occurs".

(iii) *"Caution:* Do not continue to take this product but seek medical assistance immediately if symptoms are not relieved within 1 hour or become worse".

(iv) "Do not take this product if you are presently taking a drug or suppository containing any form of theophylline except under the advice and supervision of a physician".

(v) "Do not give this product to children under 12 years except under the advice and supervision of a physician. Excessive use may cause toxic effects and even death in children".

(vi) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 12 years oral dosage based on the anhydrous theophylline equivalent is 3.33 mg/kg of body weight 3 times daily every 8 hours not to exceed 10 mg/kg in 24 hours.

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Category I Labeling

The Panel recommends the following Category I labeling for bronchodilator active ingredients to be generally recognized as safe and effective and not misbranded as well as the specific labeling discussed in the individual ingredient statements.

a. *Indications.* (1) "For temporary relief of bronchial asthma".

(2) "For symptomatic control of bronchial asthma".

(3) "Provides temporary relief from acute symptoms of bronchial asthma".

(4) "Relaxes tense bronchial muscles to ease breathing for asthma patients".

(5) "For temporary relief of wheezing (attacks and distress) of bronchial asthma".

(6) For products to be taken by inhalation: statements as to onset of action, e.g., "fast" or "quick", must be substantiated and accompanied by a specific time, e.g., "within 5 minutes".

b. *Warnings.* (1) *"Caution:* Do not take this product unless a diagnosis of asthma has been made by a physician".

2. *Category II conditions under which bronchodilator ingredients are not generally recognized as safe and effective or are misbranded.* The use of bronchodilators under the following conditions is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel concludes that the following ingredients and labeling should be removed from the market until scientific testing supports their use.

Category II Active Ingredients

The Panel has classified the following bronchodilator active ingredients as not generally recognized as safe and effective or as misbranded:

Belladonna alkaloids

Pseudoephedrine preparations: Pseudoephedrine hydrochloride, Pseudoephedrine sulfate

a. *Belladonna alkaloids by inhalation (as contained in Atropa belladonna and Datura stramonia).* The Panel concludes that belladonna alkaloids by inhalation are not safe and effective for OTC use in the treatment of asthma. The effectiveness of this preparation is unproven and it has great potential for drug abuse and toxicity. In view of the availability of other safer and effective OTC drugs for the treatment of asthma, the Panel concludes that there is no place for this preparation in the OTC treatment of asthma.

(1) *Safety.* A mixture of stramonium and belladonna is available and is utilized by smoking the cigarettes or pipe mixture or by burning the powder, like incense, and inhaling the smoke. Per unit dose (cigarette, pipeful, etc.), the alkaloid content presumably absorbed systemically is about 0.0125 mg (Refs. 1 and 2). However, the preparation is easily abused for its psychomimetic properties, by excessive use or ingestion of cigarettes, liquid suspensions or capsules filled with the powder (Ref. 2). Intoxication is generally characterized by confusion, delirium, hallucinations, and various anticholinergic effects, such as difficulty in swallowing due to dry mouth, blurred vision, photophobia, difficulty in urination, and constipation. Some deaths have been reported (Ref. 2). The adverse effects of excessive use of the powder have been well described (Ref. 3). There are numerous reports of intoxication us-

ing the powder or ingesting seeds or leaves of stramonium plants (Refs. 4 through 9). Clearly, products containing belladonna alkaloids present a risk to the consumer.

(2) *Effectiveness.* Belladonna alkaloids may be of benefit when given in the form of cigarettes (Ref. 9), but there has been no critical assessment of effectiveness. There are no well-controlled studies or other evidence to support its effectiveness as a bronchodilator when used by inhalation in the treatment of asthma.

(3) *Evaluation.* The Panel concludes that the effectiveness of belladonna alkaloids by inhalation is unproven. In view of the high potential for abuse and toxicity and the availability of other safe and effective drugs, the Panel concludes that belladonna alkaloids by inhalation are not safe and effective for OTC use in the treatment of asthma.

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(7) DeYoung and E. G. Cross, "Stramonium Psychodelia," *Canadian Anaesthetists' Society Journal,* 16:429–432, 1969.

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b. *Pseudoephedrine preparations (pseudoephdrine hydrochloride, pseudoephedrine sulfate).* The Panel concludes that pseudoephedrine preparations are safe but not effective for OTC use as a bronchodilator.

(1) *Safety.* In a study of cardiovascular effects of pseudoephedrine, dose response in four subjects showed that 210 to 240 mg (3.05 to 4.0 mg/kg) were required to raise diastolic blood pressure to 90 mm Hg or above (Ref. 1). However, a serious rise in blood pressure may occur if the drug is taken concurrently with monoamine oxidase (MAO) inhibitors (Refs. 2 and 3). Skin reactions both of long and short duration may be associated with taking the drug but these are rare (Refs. 4 and 5). Six of 21 patients who took 60 mg orally had mild side effects of drowsiness, nausea, insomnia, and headache (Ref. 6).

(2) *Effectiveness.* In a careful double-blind study using 210 mg pseudoephedrine hydrochloride orally in nine subjects with reversible obstruction to air flow, measurements were made of vital capacity and forced expiratory volume in 1 second (FEV_1), which is a measurement related to airway obstruction, the higher the figure the better the air flow and the less the obstruction in the air tubes (Ref. 1).

This high dose of pseudoephedrine increased FEV_1 to less than half that produced by ephedrine. The maximum mean percentage increased in FEV_1 was only 11 percent after pseudoephedrine and this is within the variation of the technique and not considered a significant change. Ephedrine was used in the same study and caused a 27 percent improvement in FEV_1. In another double-blind placebo-controlled study, 100 to 200 mg pseudoephedrine was given intravenously and was ineffective in 12 human subjects as a bronchodilator as judged by changes in forced vital capacity (FVC) and forced expired volume (FEV_1) (Ref. 7).

(3) *Evaluation.* Based on the two studies reviewed (Refs. 1 and 7), the Panel concludes that pseudoephedrine is ineffective for use as a bronchodilator and therefore cannot be generally recognized as effective in the treatment of asthma.

REFERENCES

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(4) Brownstein, M. H., "Fixed Eruptions Due to an Ephedrine Isomer," *Archives of Dermatology,* 97:115–119, 1968.

(5) Abramowitz, E. W. and M. H. Noun, "Ephedrine Dermatoses: Clinical and Experimental Study of a Personal Case, with a Review of the Literature," *The British Journal of Dermatology and Syphilis,* 45:225–237, 1933.

(6) Arbesman, C. E. and R. J. Ehrenreich, "New Drugs in the Treatment of Allergies," *New York State Journal of Medicine,* 61:219–229, 1961.

(7) Levy, D., S. Permutt and W. F. Russell, Jr., "An Evaluation of Three Drugs Alleged to Relieve Airway Obstruction in Asthmatic Patients," *Current Therapuetic Research* 3: 174–184, 1961.

Category II Labeling

All claims that state or imply a therapeutic action or safety property peculiar to the preparation that cannot be demonstrated in controlled studies are not acceptable. The Panel has previously discussed such labeling (See part II. paragraph O. above—CCABA Product Labeling Claims Not Supported by Scientific Evidence.). However, labeling that is descriptive of the product such as its taste or appearance are acceptable.

The Panel concludes that the following labeling is misleading and contains unacceptable claims for preparations used for the treatment of asthma. The Panel assumes that preparations under consideration will contain only a sympathomimetic of the bronchodilator type and/or theophylline ingredients. The Panel believes that the language expressed in the following misleading claims is excessive and claims either too much or claims effects which do not occur. For example, most asthma preparations have no effect on hay fever, the nose, the "common cold", or on congestion. The following apply regardless of whether the preparation is given by inhalation or by mouth:

a. *Unacceptable labeling because these claimed effects do not occur with bronchodilators.* (1) "Relief of hay fever".

(2) Claims for any effects "on nasal passages".

(3) Statements related to "congestion of air tubes or lungs".

(4) "Decongests swollen membranes, acts to loosen congestion, relief of general respiratory congestion".

(5) "Relief of bronchitis or 'the common cold' ".

(6) "Relief of fear, anxiety, nervous tension".

(7) "Cleans bronchial passages".

(8) "Contains anti-allergen ingredient".

(9) "Eases irritation of bronchial and nasal mucous membranes, and itchy, watery eyes".

(10) "Relief of other respiratory conditions".

(11) "Phlegm broken up and one is able to expel the phlegm with little effort".

(12) "Nagging cough is reduced to a minimum and as a result sleep is much deeper and uninterrupted".

b. *Unacceptable labeling because of the difficulty to substantiate and the implication that high use rate is evidence of the particular effectiveness of the ingredients.* "Most prescribed or recommended by doctors in medical practice".

c. *Unacceptable labeling because the claim suggests it is particularly effective.* "Proved highly effective in medical practice". The Panel notes that effectiveness must already be established to be classified as Category I.

d. *Unacceptable labeling because the claim is excessive and difficult to substantiate.* "Effective when all other available means have failed".

e. *Unacceptable labeling because excessive claims are made in emotional terms.*

(1) "Relieves gasping for air".

(2) "Free breathing restored".

(3) "Breathes a sigh of relief".

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel concludes that adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed ingredient and conditions listed below. The Panel believes it is reasonable to provide 3 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within 3 years, however, the ingredient and conditions listed in this category should no longer be marketed in over-the-counter products. Effectiveness as a bronchodilator must be demon-

strated by controlled objective studies. Subjective data alone are unacceptable because of the marked variability in the subjective awareness of the wheezing and shortness of breath associated with asthma.

Category III Active Ingredient

The Panel concludes that the available data are insufficient to permit final classification of the following claimed bronchodilator active ingredient.

The Panel concludes that there is insufficient evidence that euphorbia pilulifera is effective as a bronchodilator.

a. *Safety.* Clinical experience has confirmed that euphorbia pilulifera is safe in the dosage ranges used as a bronchodilator. In large dosage, it is said to be an irritant to the gastric mucous membrane (Ref. 1). There is some disagreement as to its effect on the skin. In one reference it is said not to irritate the skin (Ref. 1), but in others it is said to produce vesication (Refs. 2 and 3). It produces an increase in bronchial secretion, and large doses cause vomiting and diarrhea. Limited animal experiments showed no serious side effects (Ref. 4). Marketing experience of a capsule product has resulted in no serious complaints (Ref. 4).

b. *Effectiveness.* There are no well-controlled studies documenting the effectiveness of euphorbia pilulifera as a bronchodilator. The drug has been used in the treatment of asthma and bronchitis but "its value is not apparent" (Ref. 5). In Pharmacotherapeutics, 1928, (Ref. 2) it stated: "It finds some use as a bronchodilator in spasmodic asthma and in chronic bronchitis." It has been employed as a constituent of cough mixtures containing more active drugs and it has occasionally been employed in small dose in the treatment of the "common cold" and hay fever (Ref. 2). It has been marketed in a dosage of 0.715 gm in combination with aspirin and caffeine as a capsule, and many patients have claimed relief from asthma, sinusitis, bronchitis, hay fever, and rhinitis as well as good results in colds (Ref. 4). However, there is no evidence from the references that the drug has ever had any type of scientific testing.

c. *Proposed dosage.* The Panel is unable to determine a proposed dosage. Euphorbia pilulifera has been used as an elixir, fluidextract, tincture, in capsule and powder form, and as leaves to be smoked. The dosages are as follows: Elixir euphorbiae compositum (National Formulary) 4 to 46 mg followed by 92 mg twice daily for not more than a total of 3 doses daily; 8 ml fluidextractum euphorbiae (National Formulary) 1 to 3 ml; and tinctura euphorbiae (unofficial) 0.6 to 1.8 ml; powder 0.6 to 4 gm; and capsule (no dose could be determined). These dosages are recommended in the literature (Refs. 2 and 6). There are no details regarding frequency of dosage.

The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

d. *Labeling.* The Panel recommends the Category I labeling for bronchodilator active ingredients. (See part V. paragraph C. below—Category I Labeling.)

e. *Evaluation.* Data to demonstrate effectiveness as a bronchodilator will be required in accordance with the guidelines set forth below for testing bronchodilator drugs. (See part V. paragraph C. below—Data Required For Evaluation.)

REFERENCES

(1) "The Dispensatory of the United States of America," 25th Ed., Edited by Osol, A. and G. E. Farrar, J. B. Lippincott Co., Philadelphia, p. 1688, 1960.

(2) Solis-Cohen, S. and T. S. Githens, "Pharmacotherapeutics, Materia Medica and Drug Action," D. Appleton and Co., New York, p. 1391, 1928.

(3) Culbreth, D. M. R., "A Manual of Materia Medica and Pharmacology," 7th Ed., Lea and Febiger, Philadelphia, p. 372, 1927.

(4) OTC Volume 040211.

(5) Hellerman, R. C. and L. W. Hazelton, "The Antispasmodic Action of Euphorbia Pilulifera," *Journal of the American Pharmaceutical Association (Scientific Edition)*, 39:142–146, 1950.

(6) "The Merck Index," 5th Ed., Merck and Co., Inc., Rahway, New Jersey, p. 232, 1940.

Category III Labeling

The Panel concludes that the available data are insufficient to permit final classification of the labeling claim identified below for bronchodilators. Additional data are required to support the following bronchodilator claim: "For temporary relief of cough caused by the 'common cold' or 'bronchitis'". The Panel concludes that the effect of bronchodilators on cough (other than due to asthma) is uncertain.

C. DATA REQUIRED FOR EVALUATION

The Panel has agreed that the protocols recommended in this document for the studies required to substantiate Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. *Principles in the design of an experimental protocol for testing bronchodilator drugs.* a. *General principles.* The effectiveness of a bronchodilator drug is determined by its ability to reverse the airway obstruction of patients with asthma. Although clinical improvement may be reported, it is essential to have objective measurements of pulmonary function to substantiate improvement. Tests of bronchodilator drugs should be double-blind and crossover studies. Pulmonary function tests should be performed before and after the drug or placebo is given. Objective testing should be done for a sufficient time to show the duration of action of the drug. For OTC drugs a single dose should be shown to be effective. Continual taking of the drug over days or weeks to show improvement is not acceptable for OTC products. The patient needs to get quick and obvious relief from a single dose. The drugs used should be tested in the same dosage as the purchaser might be expected to take, i.e., the recommended dosage on the label.

To show effectiveness it is necessary for two studies by two different investigators to indicate that there is definite improvement in pulmonary function following single doses of the drug under test as described under Interpretation of data, below.

b. *Selection of patients.* Selection of patients for testing should be based on the diagnosis of asthma. There should be generalized airway obstruction whose severity varies greatly over short periods of time, and this should be demonstrated by pulmonary function tests improving significantly after the use of an accepted bronchodilator drug.

c. *Methods of study.* For large series of patients, the forced vital capacity, forced expiratory volume (one second), and maximal midexpiratory flow rate are the simplest and most available tests. However, measurements of flow from flow-volume curves at 50 percent and 75 percent of the vital capacity, measurements of airway resistance and specific conductance using a body plethysmograph are recommended when the complex equipment is available.

The precise number of patients to be tested cannot be stated. However, if the drug is effective, approximately 20 patients should be sufficient for satisfactory statistical analysis of data.

d. *Interpretation of data.* Ideally, the response should be interpreted according to the recognized variability in the laboratory in which the test is being performed. Where such variability is not precisely defined, improvement of 15 to 25 percent may be considered a slight reversibility; a change of 26 to 50 percent is moderate reversibility; and greater than 50 percent is marked reversibility. However, for the purposes of an experimental protocol, statistical analysis and significance is essential.

Evidence of drug effectiveness is required from a minimum of two positive studies based on the results of two different investigators or laboratories.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

e. *Evaluation of safety.* Tests of safety should involve the usual tests for toxicity to the respiratory system and be relevant to the known possible adverse effects of the drugs under testing. Tests should be done in the form of dose response curves up to maximum therapeutic effectiveness.

REFERENCE

(1) Woolf, C. R., R. Kory and J. Ross, "Criteria for the Assessment of Reversibility in Airway Obstruction," *Chest*, 65:552–553, 1974.

VI. ANTICHOLINERGICS

A. GENERAL DISCUSSION

Anticholinergics are drugs used in the symptomatic relief of excessive secretions of the nose (rhinorrhea) and eyes commonly associated with hay fever, allergy, rhinitis and the "common cold." The tissues responsible for these secretions, the glands of the nasal mucosa and

the lacrimal glands, are supplied by nerves known as cholinergic or parasympathetic nerves. These nerves release a neurohumoral substance, acetylcholine (ACh), which acts on receptors in these tissues apparently causing the excessive secretions. The anticholinergic drugs, by competing with ACh for these receptors, reduce or prevent the secretions.

There are other tissues having receptors acted on by ACh, and the anticholinergic drugs are able to prevent the response usually caused by ACh at these sites as well. These other tissues are the sweat, salivary and bronchial glands, the muscles for visual accommodation (adaptation of the eye for distinct vision at different distances), the heart, the gastrointestinal tract, and the urinary bladder. The cholinergic nerves which innervate these tissues are compositely known as the parasympathetic nervous system. All these tissues are not equally sensitive to the anticholinergic agents and the responses are dose related. Small doses depress salivary bronchial and sweat secretions. Larger doses are required to inhibit visual accommodation or increase the heart rate. Still larger doses are required to inhibit the parasympathetic control of the gastrointestinal tract or the urinary bladder.

The naturally occurring anticholinergic drugs, the alkaloids of the belladonna plants, are widely distributed in nature especially among the Solanaceae. The active drugs derived from these plants are atropine (dl-hyoscyamine) and scopolamine (l-hyoscine) depending upon which plant is the source. The official preparations of belladonna act chiefly by virtue of their atropine content.

Atropine is the classical representative of this group of anticholinergic drugs. It is dl-hyoscyamine, the stereoisomers being present in equal amounts but the activity residing in the l-form. The drying effect on the respiratory tract may be useful in the symptomatic relief of excessive secretions of the nose (rhinorrhea) and eyes commonly associated with hay fever, allergy, rhinitis and the "common cold." The effect of atropine is most noticeable if there are excessive secretions. There is no evidence that the course of the illness is altered by these drugs. At higher doses, the bronchi and bronchioles (large and small airways) are relaxed. This relaxation is most pronounced if the bronchi and bronchioles are contracted by histamine or increased parasympathetic activity and the atropine is administered by inhalation.

These drugs reduce the volume of secretions as well as making them less fluid. The less fluid secretions are more difficult to remove from the respiratory passages and may lead to obstruction. This predisposes the patient to infection. In a person with bronchial asthma or chronic obstructive pulmonary disease, this may be extremely hazardous.

The belladonna alkaloids will have little effect on the intraocular pressure of the normal eye. However, in the glaucomatous eye, when the intraocular pressure is initially above normal, they are likely to increase the intraocular pressure and damage the eye, especially in narrow angle glaucoma.

The toxic or side effects of the anticholinergic drugs are an extension of the pharmacologic effects of the drugs. These effects are dry mouth, anhydrosis, tachycardia, dilatation of the pupil and blurred vision, photophobia, restlessness, confusion and difficulty in urination. Very large doses may cause elevated body temperature and respiratory depression. Elderly men with enlargement of the prostate gland may develop urinary obstruction with less than toxic doses. There are numerous synthetic anticholinergic compounds, none of which differ significantly in pharmacologic effects or toxic effects from the naturally occurring drugs. Antihistaminics in varying degrees also have an anticholinergic effect. Antihistamines are discussed in another section of this document. (See part VII. below—Antihistamines.) Given together with an anticholinergic in the same preparation or at the same time, an antihistaminic drug will have at least an additive anticholinergic effect. With this in mind, the dose of each should be adjusted accordingly.

REFERENCES

(1) Innes, I. R. and M. Nickerson, "Drugs Inhibiting the Action of Acetylcholine on Structures Innervated by Postganglionic Parasympathetic Nerves (Antimuscarinic or Atropinic Drugs)," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. A. and A. Gilman, MacMillan Co., New York, pp. 524–548, 1970.

(2) "Drill's Pharmacology in Medicine," 4th Ed., Edited by DiPalma, J. R., McGraw-Hill, pp. 608–626, 1971.

B. CATEGORIZATION OF DATA

1. *Category I conditions under which anticholinergic ingredients are generally recognized as safe and effective and are not misbranded.*

Category I Active Ingredients

The Panel was unable to classify a claimed anticholinergic active ingredient as generally recognized as safe and effective and not misbranded.

Category I Labeling

The Panel recommends the following Category I labeling for anticholinergic active ingredients to be generally recognized as safe and effective and not misbranded:

a. *Indications.* (1) "For temporary relief of watery nasal discharge and watering eyes as may occur in certain allergic conditions and infections of the upper respiratory tract".

(2) "Temporarily suppresses watery nasal discharge".

(3) "Temporary relief from excessive nasal secretions".

(4) "Temporary relief from running nose".

(5) "Temporarily suppresses watering of eyes".

b. *Warnings.* (1) "Do not exceed recommended dosage except under the advice and supervision of a physician".

(2) "Do not continue to take this product if constipation, excessive dryness of the mouth, insomnia, excitement, confusion, rapid pulse, or blurring of vision occur".

(3) "*Caution:* Do not take this product if you have asthma, glaucoma or have difficulty in urination due to enlargement of the prostate gland except under the advice and supervision of a physician".

(4) "Do not give this product to children under 12 years except under the advice and supervision of a physician".

2. *Category II conditions under which anticholinergic ingredients are not generally recognized as safe and effective or are misbranded.* The use of anticholinergics under the following conditions is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel concludes that the following ingredients and labeling should be removed from the market until scientific testing supports their use.

Category II Active Ingredients

The Panel has classified the following anticholinergic active ingredient as not generally recognized as safe and effective or as misbranded:

The Panel concludes that belladonna alkaloids (as contained in Atropa belladonna and Datura stramonia) when used by inhalation are not safe and effective for OTC use in asthma. The effectiveness of this preparation is unproven and it has great potential for drug abuse and toxicity. In view of the availability of other, safer, effective OTC drugs for the treatment of asthma, the Panel concludes that there is no place for this preparation in the OTC treatment of asthma.

a. *Safety.* The Panel has discussed the safety of belladonna alkaloids by inhalation in reference to the treatment of asthma with bronchodilators. (See part V. paragraph B.2.a. above—Belladonna alkaloids by inhalation (as contained in Atropa belladonna and Datura stramonia).)

b. *Effectiveness.* The Panel has discussed the effectiveness of belladonna alkaloids by inhalation in reference to the treatment of asthma with bronchodilators. (See part V. paragraph B.2.a. above—Belladonna alkaloids by inhalation (as contained in Atropa belladonna and Datura stramonia).)

c. *Evaluation.* The Panel concludes that the effectiveness of belladonna alkaloids by inhalation is unproven. In view of the high potential for abuse and toxicity and the availability of other drugs, the Panel concludes that belladonna alkaloids by inhalation are not safe and effective for OTC use as an anticholinergic.

Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety and/or effectiveness of the product are unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel has previously discussed such labeling. (See part II. paragraph O. above—CCABA Product Labeling Claims Not Supported by Scientific Evidence.) However, labeling that is descriptive of the product such as its taste or appearance is acceptable.

The Panel concludes that the following claims are misleading and are unacceptable for preparations used as anticholinergics:

a. *Claims not supported by scientific data.* "Clears nasal passages, open airways".

b. *All claims which state or imply a therapeutic action or safety property peculiar to the preparation that cannot be demonstrated in controlled studies.* These include claims such as "specially formulated", "scientifically improved or selected", "natural", "extra strength", "teamed components", "superior to ordinary", also claims implying a physiological effect which either has no foundation or meaning or will be meaningless or misleading to the public such as "antiallergic", "gets at the roots of", "fights", "wakes up", "recommended by doctors", and "travels through the blood stream".

c. *Claims for relief where time is indeterminate, and not supported by scientific data.* These include claims such as "all day", "all night", "for hours", "fast", and "prompt".

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel concludes that adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed ingredients and conditions listed below. The Panel believes it reasonable to provide 3 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within 3 years, however, the ingredients listed in this category should no longer be marketed as over-the-counter products. Effectiveness as an anticholinergic must be demonstrated by the ability to reduce rhinorrhea in patients with acute or chronic rhinitis. The evaluation must be a subjective study since the Panel is unaware of any technique for objective measurements.

Category III Active Ingredients

The Panel concludes that the available data are insufficient to permit final classification of the following claimed anticholinergic active ingredients: Atropine sulfate, Belladonna alkaloids.

a. *Atropine sulfate.* The Panel concludes that atropine sulfate is probably safe in the dosage range currently used (0.2 mg to 0.3 mg) as an anticholinergic but there are insufficient data to permit final classification of its effectiveness for OTC use as an anticholinergic. Although atropine at a higher dose, 0.6 mg, may be effective in relieving excessive secretions of the nose, there is no evidence that smaller doses as used in OTC preparations will do this. However, the Panel recommends that atropine not be made available for OTC use at a 0.6 mg dosage until suitable studies have been completed to show safety.

(1) *Safety.* Clinical experience has confirmed that atropine sulfate is probably safe in adults when taken orally as an anticholinergic in the currently marketed OTC dose of 0.03 mg to 0.2 mg total belladonna alkaloids. Dryness of the mouth appears first at about 0.5 mg (Ref. 1). No adverse effect was found in patients with open angle glaucoma taking 0.6 mg 3 times daily for 7 days (Ref. 2). Suppression of salivation occurred in children at the following oral doses: 1 to 12 months, 0.016 mg/kg; 12 to 36 months 0.014 mg/kg; 3 to 6 years, 0.022 mg/kg; and 6 to 12 years, 0.02 mg/kg (Ref. 3). A 7-week infant took more than 40 mg in 24 hours and recovered (Ref. 4). Ingestion of 450 mg in an adult has been followed by recovery (Ref. 5). There is a lack of data to support the use of anticholinergic active ingredients in children under the age of 12. The Pediatric Consultant Panel recommended that no dosage be marketed for children until further studies were completed. (See part II. paragraph H. above—Pediatric dosage.)

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of atropine sulfate as an anticholinergic. In the treatment of excessive secretions of the nose associated with the "common cold," atropine appears to be ineffective, but only one study is available (Ref. 6). The study indicated that a dose of 0.6 mg given early may transiently reduce the nasal secretions associated with the "common cold" giving some temporary comfort. However, there is no evidence that the very small doses of belladonna alkaloids per dosage unit in currently marketed OTC preparations, i.e., 0.03 to 0.2 mg total alkaloids, are effective.

(3) *Proposed dosage.* The Panel is unable to determine a proposed dosage. Although 0.6 mg atropine sulfate may be effective, the Panel concludes that such a dosage should not be available for OTC use until studies demonstrate safety. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product. In such a case, the Panel concludes that for children under 12 years, there be no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for anticholinergic active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing anticholinergic drugs. (See part VI. paragraph C. below—Data Required for Evaluation.)

REFERENCES

(1) Gowdy, J. M., "Stramonium Intoxication," *Journal of the American Medical Association,* 221:585–587, 1972.

(2) Lazenby, G. W., J. W. Reed and W. M. Grant, "Anticholinergic Medication in Open-Angle Glaucoma," *Archives of Ophthalmology,* 84:719–723, 1970.

(3) Unna, K. R., K. Glaser, E. Lipton and P. R. Patterson, "Dosage of Drugs in Infants and Children: I. Atropine," *Pediatrics,* 6:197–207, 1950.

(4) Joos, H. A., "Atropine Intoxication in Infancy," *American Journal of Diseases of Children,* 79:855–861, 1950.

(5) Comroe, B. I., "Atropine Poisoning: Recovery After 7½ Grains of Atropine Sulfate by Mouth," *Journal of the American Medical Association,* 101:443–447, 1933.

(6) Personnel of the U.S. Naval Medical Research Unit No. 4, "The Prophylaxis and Treatment of Acute Respiratory Diseases with Antihistaminic Drugs," *Journal of Laboratory and Clinical Medicine,* 36:555–569, 1951.

b. *Belladonna alkaloids.* The Panel concludes that the belladonna alkaloids are probably safe in the dosage range used as anticholinergics but there are insufficient data to permit final classification of their effectiveness for OTC use as anticholinergics.

(1) *Safety.* Clinical experience has confirmed that belladonna alkaloids are safe in the dosage ranges used as anticholinerics. The belladonna alkaloids contain atropine (d, dl hyoscyamine) and scopolamine (l-hyoscine) and are present in official preparations, e.g., belladonna tincture United States Pharmacopoeia (USP) and belladonna extract National Formulary (NF). These preparations act by virtue of their atropine content. Scopolamine is approximately 10 percent of the total alkaloid content and has the same pharmacological effect and toxicity as atropine, but is slightly more potent. The Panel has discussed the safety of atropine elsewhere in this document. (See part VI. paragraph B.3.a. above—Atropine sulfate.)

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of belladonna alkaloids as anticholinergics. Atropine and other belladonna alkaloids and substitutes reduce secretion in both the upper and the lower respiratory tract, and they are common constituents of proprietary "cold" tablets (Ref. 1). This effect in the nasopharynx may provide some symptomatic relief of acute rhinitis associated with conditions such as coryza or hay fever. However, there are no controlled studies to support this hypothesis.

The belladonna alkaloids can induce bronchial dilatation. This is particularly marked when they are administered by inhalation, but it is still less than can be achieved by other types of medication.

All antimuscarinic agents reduce the volume of bronchial secretion which results in decreased fluidity and inspissation of the residual secretion. This viscid material is difficult to remove from the respiratory tree, and its presence can dangerously obstruct airflow and predispose to infection. Because of the effect on bronchial secretion, repeated administration of any antimuscarinic to a patient with chronic lung disease must be considered as potentially hazardous.

(3) *Proposed dosage.* Adult oral dosage is 0.2 mg 2 times daily. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for anticholinergic active ingredients. (See part VI. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for anticholinergic drugs. (See part VI. paragraph C. below—Data Required for Evaluation.)

REFERENCE

(1) Innes, I. R. and M. Nickerson, "Drugs Inhibiting the Action of Acetylcholine on Structures Innervated by Postganglionic Parasympathetic Nerves (Antimuscarinic or Atropinic Drugs)," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, p. 542, 1970.

Category III Labeling

The Panel concludes that the available data are insufficient to permit final classification of the labeling claim identified below for anticholinergics. Additional data are required to support the following anticholinergic claim: a. "Prolongs relief by helping to prevent further swelling and irritation."

b. The Panel concludes that claims relating to duration of action, e.g. "all day", "all night", "for hours", will require documentation.

c. *Claims that sleep will be facilitated.* These include claims such as "helps you fall asleep" and "for restful sleep".

C. DATA REQUIRED FOR EVALUATION

The Panel has agreed that the protocols recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. *Principles in the design of an experimental protocol for testing anticholinergic drugs.* a. *General principles.* The effectiveness of an anticholinergic drug should be determined by the ability to reduce rhinorrhea (excessive watery nasal secretions) in patients with acute or chronic rhinitis. Tests should involve double-blind placebo controlled assessment of the ability of the drug to decrease watery nasal secretions and/or tearing when administered orally and increase the comfort of the patient. This evaluation must be a subjective one since there is no technique for objective measurements. The dosage, intervals of administration and conditions for the trials should be identical to the labeled recommendations.

b. *Selection of patients.* Selection of patients for treatment should be based on the diagnosis of rhinitis with rhinorrhea. Patients with chronic allergic or vasomotor rhinitis may present more stable symptoms but in most patients rhinorrhea is a variable and inconstant symptom. Because of this, a large number of suitable patients, e.g., approximately 50 subjects depending upon the protocol, must be used and assigned in a random fashion to placebo or drug groups. Further, these groups should be matched by age and sex, and if possible, by severity of symptom. It is also highly desirable to control conditions of temperature and humidity.

c. *Methods of study.* There is nothing in the literature concerning techniques for testing rhinorrhea and it is possible that a subjective method could be developed. It might be possible to semiquantitate the degree of rhinorrhea by weighing tissues or handkerchiefs; the wet weight minus the dry weight would be a rough index of the amount of secretions per unit of time. The subjects should be evaluated on the basis of the severity of the rhinorrhea and the subject's appraisal of his discomfort. Numerical values should be assigned indicating increasing severity. A double-blind technique is used for patients with acute rhinitis and in chronic rhinitis with rhinorrhea a double-blind crossover design. Observation should be carried out for 3 to 5 days to determine the extent of possible side effects.

d. *Interpretation of data.* The data should be subjected to statistical analysis and a p value of 0.05 or less would be acceptable as evidence of drug action.

Evidence of drug effectiveness is required from a minimum of three positive studies based on the results of three different investigators or laboratories.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

e. *Evaluation of safety.* Tests of safety should involve the usual tests for toxicity relevant to the known possible adverse effects of the drugs under testing. Tests should be done in the form of dose-response curves up to maximum therapeutic effectiveness.

VII. ANTIHISTAMINES

A. GENERAL DISCUSSION

1. *Development.* The antihistamines were developed in France from a series of compounds with pronounced antihistaminic activity in the laboratory but which were too toxic for clinical use. One of these antihistaminic drugs, Antergan, was used for the first time clinically in 1942 in France. This was promptly followed by pyrilamine maleate. There then followed in 1946 the appearance in the United States of diphenhydramine and tripelennamine (Ref. 1). Many active antihistamine drugs appeared soon thereafter and the total number currently marketed is probably now close to fifty.

REFERENCE

(1) Loew, E. R., "Pharmacology of Antihistamine Compounds," *Physiological Reviews*, 27:542–573, 1947.

2. *Mechanism of action.* The antihistamines are useful primarily for the symptomatic relief of certain allergic disorders (Refs. 2 through 5). They suppress symptoms presumably caused by the release of histamine and possibly other chemical mediators from mast cells in mucous membranes (Refs. 1, 2, 5, and 6). Histamine attaches to specific receptor sites at the surface of cells in the nose, eyes, lungs, and skin and causes characteristic "allergic" symptoms. The antihistamines appear to act by competing with histamine for the receptor sites. If the antihistamine reaches the receptor site first, histamine is blocked from initiating a response. In this manner, antihistamines effectively block most smooth muscle responses to histamine.

The antihistaminic drugs are well tolerated by laboratory animals and produce recognizable effects on blood pressure, heart rate or respiration when given in large oral doses. These effects are more pronounced if the drugs are given intravenously (Refs. 2 and 5).

In man, the involvement of renal (kidney), hepatic (liver), hematologic (blood) or other major body systems in adverse reactions appears to be remarkably uncommon (Refs. 5 and 7).

In the skin of man, antihistamines inhibit the wheal, flare and itch reaction that occurs within a few minutes after the injection of histamine intracutaneously (into the skin). The antihistaminic drugs also inhibit similar reactions mediated by antibodies belonging to the IgE class of immunoglobulins (antibodies), but to a somewhat lesser degree. The Panel has previously discussed the role of antibodies in allergy earlier in this document. (See part II. paragraph B.1. above—Allergy.) Examples of reactions mediated by antibodies of the IgE class are those produced by skin testing with pollen extracts in which histamine release is involved. In addition to histamine, there are other chemical mediators released in IgE mediated reactions, and the antihistaminic drugs antagonize these much less effectively if at all. It is probably for this reason that these drugs are more active in protecting against the effects of injected histamine than in protecting against anaphylaxis in animals or allergic symptoms in man.

REFERENCES

(1) Loew, E. R., "Pharmacology of Antihistamine Compounds," *Physiological Reviews*, 27:542–573, 1947.

(2) Douglas, W. W., "Histamine and Antihistamines; 5-Hydroxytryptamine and Antagonists," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, pp. 635–642, 1970.

(3) "AMA Drug Evaluations," 2d Ed., Publishing Sciences Group, Incorporated, Action, Massachusetts, pp. 491–492, 1973.

(4) "Antihistamine Drugs," *in* "American Hospital Formulary Service," The American Society of Hospital Pharmacists, Washington, D.C., 4:00, 1975.

(5) Beckman, H., "Pharmacology; The Nature, Action and Use of Drugs," 2d Ed., The W. B. Saunders Co., Philadelphia, 1961.

(6) Roth, F. E. and I. I. A. Tabachnick, "Histamine and Antihistamines," *in* "Drill's Pharmacology in Medicine," 4th Ed., Edited by Dipalma, McGraw Hill Co., New York, pp. 995–1020, 1971.

(7) Wyngaarden, J. B. and M. H. Seevers, "The Toxic Effects of Antihistamine Drugs," *Journal of the American Medical Association*, 145:277–282, 1951.

3. *Preclinical studies.* As a group the antihistamines have the capacity to decrease or suppress effects produced by histamine in animals (Refs. 1 through 4). Animal "models" are therefore useful in determining drugs which will have antihistamine activity. An animal commonly used is the guinea pig. Guinea pigs can be protected by an antihistaminic drug from the often fatal narrowing of the air passages in the lung (bronchoconstriction) produced by histamine which causes death by asphyxia. Likewise, contraction of isolated tissues

of the guinea pig intestine (ileum) and of the airways of the trachea and bronchus produced by histamine is prevented by antihistamines in in vitro studies. These effects are most easily demonstrated in the guinea pig because of the animal's intense sensitivity to histamine but the antihistaminic drugs also act in a similar manner in some other laboratory animals and in man (Refs. 1 through 3).

The antihistaminic drugs are somewhat protective in experimental allergic reactions (anaphylaxis) but their action here is not so intense as their action against histamine. Apparently in man, some allergic reactions (hay fever and hives) are caused entirely or in large part by histamine release whereas other reactions, for example asthma, are not. The capacity to block the symptom-producing effects of histamine presumably explains why antihistamines are effective in relieving the symptoms of hay fever and hives (consisting of rashes associated with itching wheals) in which release of histamine appears to be the main cause of the symptoms (Refs. 2 and 3).

In concentrations that are effective against the spasmogenic activity of histamine, antihistamines have little or no capacity to counter the spasmogenic activity of other drugs such as acetylcholine, nicotine or barium.

Gastric ulcers with perforation have occurred in guinea pigs receiving both histamine and antihistamine under highly artificial conditions (Ref. 3). The experiment depends on the fact that antihistamine drugs can protect against histamine-induced bronchospasm and asphyxia although the antihistaminic drugs do not prevent another action of histamine which is to stimulate the production of acid within the stomach. Under the conditions of the experiment, increased acid production is induced in the guinea pig by giving large doses of histamine. The antihistamine protects the guinea pig from bronchospasm and fatal asphyxia which the histamine would otherwise cause. The Panel finds, therefore, that the antihistaminic drugs play no ulcer-producing role in this type of experiment and there are no other data which would implicate the antihistaminic drugs in promoting acid production in the stomach or ulcer.

In view of the chemical heterogeneity of the antihistamines, there is a surprising unanimity among the statements of critical investigators and authorities in describing their antihistaminic actions. The antihistamines under consideration are described as being intense antagonists of histamine, are of low acute (Ref. 1) and chronic (Ref. 2) toxicity and most are effective in suppressing the symptoms of allergic rhinitis (Refs. 1, 2, 3, 5, and 6). It is because these attributes are shared by most or all of the antihistamine drugs that individual drugs are not often singled out for special attention in the texts reviewed.

REFERENCES

(1) Roth, F. E. and I. I. A. Tabachnick, "Histamine and Antihistamines," *in* "Drill's Pharmacology in Medicine," 4th Ed., Edited by Dipalma, J., McGraw-Hill Co., New York, pp. 995–1020, 1971.

(2) Beckman, H., "Pharmacology; The Nature, Action and Use of Drugs," 2d Ed., The W. B. Saunders Co., Philadelphia, 1961.

(3) Douglas, W. W., "Histamine and Antihistamines; 5-Hydroxytryptamine and Antagonists," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, pp. 635–642, 1970.

(4) Loew, E. R., "Pharmacology of Antihistamine Compounds," *Physiological Reviews*, 27:542–573, 1947.

(5) "AMA Drug Evaluations," 2d Ed., Publishing Sciences Group, Incorporated, Acton, Massachusetts, pp. 491–492, 1973.

(6) "Antihistamine Drugs," *in* "American Hospital Formulary Service," The American Society of Hospital Pharmacists, Washington, D.C., 4:00, 1975.

4. *Common side effects.* Among the antihistamines, there are minor differences in the nature and frequency of side effects and toxicity which are related to chemical class (Refs. 1 through 3). With the exception of phenindamine, all the antihistamines considered by the Panel cause central nervous system depression, often recognized as drowsiness (sedation). Drowsiness is most marked among the antihistamines from the chemical class known as the ethanolamines, e.g., diphenhydramine, doxylamine and phenyltoloxamine, and least marked among the alkylamines, e.g., chlorpheniramine, brompheniramine and pheniramine. The ethylenediamines, e.g., methapyrilene, pyrilamine maleate, thenyldiamine and thonzylamine, are intermediate in this respect.

There is a wide range of susceptibility to actions of the antihistaminic drugs especially as regards the central nervous system. The chief danger from overdosage of antihistamines is central nervous system depression. The ethanolamines, (e.g., diphenhydramine and doxylamine) and the ethylenediamines, (e.g., methapyrilene) are also used as mild sleep inducers, and the ethanolamines, (e.g., diphenhydramine and dimenhydrinate) and the ethylenediamines, (e.g., methazine) as antiemetics for the treatment of the symptoms of motion sickness. Some are useful in treating paralysis agitans and petit mal seizures. No exact explanation for these actions is available.

Stimulation of the central nervous system has been observed in patients with focal cortical lesions in whom small doses of antihistamines may cause electroencephalographic activity and even frank seizures (Ref. 4). However, the precise basis for this stimulation is not fully understood. Excessive doses in any patient may cause restlessness, excitation, delirium, tremors, and even convulsions (Refs. 1 through 3). Phenindamine causes stimulation rather than depression as a common side effect and is unique in this respect among the antihistamines under consideration. The Panel has discussed this side effect observed with phenindamine later in this document. (See part VII. paragraph B.1.f. below—Phenindamine tartrate.)

Dryness of the mouth is also a common side effect of the antihistaminic drugs. Other side effects which are not as common as drowsiness have been reported in scientific texts but are poorly documented and often cannot be definitely ascribed to antihistamines. These include gastrointestinal effects such as anorexia (appetite loss), nausea, vomiting, epigastric distress, constipation or diarrhea (Ref. 1).

Also reported are cardiovascular symptoms which may include palpitations, hypotension, headache or tightness of the chest (Ref. 1). In the genitourinary system, an effect on the frequency of urination and/or dysuria may be encountered (Ref. 1). Cutaneous side effects such as urticarial, eczematous, bullous, or petechial rashes and photosensitivity may occur (Ref. 5). Hematologic complications that have been reported have included rare occurrences of pancytopenia, thrombocytopenia, hemolytic anemia and agranulocytosis (Ref. 5).

The Panel concludes that serious side effects produced by the antihistaminic drugs in the dosages recommended for OTC use are rare and the more common side effects are rarely serious.

REFERENCES

(1) Douglas, W. W., "Histamine and Antihistamine; 5-Hydroxytryptamine and Antagonists," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, pp. 635–642, 1970.

(2) Beckman, H. "Pharmacology; The Nature, Action and Use of Drugs," 2d Ed., The W. B. Saunders Co., Philadelphia, 1961.

(3) Roth, F. E. and I. I. A. Tabachnick, "Histamine and Antihistamines," *in* "Drill's Pharmacology in Medicine," 4th Ed., Edited by Dipalma, J., McGraw-Hill Co., New York, pp. 995–1020, 1971.

(4) King, G. and S. D. Weeks, "Pyribenzamine Activation of the Encephalogram, EEG," *Clinical Neurophysiology*, 18:503, 1965.

(5) "AMA Drug Evaluations," 2d Ed., Publishing Sciences Group, Incorporated, Acton, Massachusetts, pp. 491–492, 1973.

5. *Reduction of nasal secretions.* A common but variable action of the antihistaminic drugs is their anticholinergic effect of reducing nasal secretions. Some patients describe this as a disagreeable drying effect. In the recommended dosage, the drying effect of most antihistamines is less intense than that of atropine. This action appears to be entirely palliative and does not alter or shorten the course of the illness. The Panel is aware that a controversy exists concerning the use of antihistamines in patients with bronchial asthma where a "drying action" is undesirable. Many physicians consider this effect to be disadvantageous in patients with bronchial asthma and some maintain that the antihistaminic drugs are contraindicated in patients with this disease.

It is the view of the Panel that in the presence of allergic rhinitis and in the "common cold," secretions are often excessive and a "drying" agent may then be appropriate. However, the Panel finds, as do other investigators, that effectiveness of antihistamines widely used in the "common cold" has not been demonstrated in controlled studies (Ref. 1). In

addition, the Panel concludes that there is no evidence that release of histamine is either the cause of symptoms in the "common cold" nor is histamine release a significant factor in the "common cold." This will be discussed more fully below. (See part VII. paragraph C.2. below—Principles in the design of an experimental protocol for testing antihistamine drugs in the "common cold.")

REFERENCE

(1) West, S., B. Brandon, P. Stolley and R. Rumrill, "A Review of Antihistamines and the Common Cold," *Pediatrics*, 56:100–107, 1975.

6. *Human toxicity.* Unlike other classes of drugs, the extensive clinical experience with antihistamines has fairly well identified virtually all of the central nervous system manifestations of toxicity. The Panel has extensively reviewed these known toxic symptoms. While many of the more severe symptoms of antihistamines are relatively rare or are due to large doses or accidental overdose, the Panel has included them in the interest of completeness of this review.

Although rare, fatal or near fatal doses cause fixed, dilated pupils; muscular twitching followed by convulsions, sometimes with opisthotonos; coma; circulatory collapse; and respiratory failure. Convulsions may persist for 24 hours, coma for several days. Death rarely occurs later than 24 hours after ingestion unless due to infection associated with agranulocytosis (Ref. 1).

Because of the unique nature and wide use of antihistaminic drugs and because of the lack of extensive well-controlled clinical studies, the Panel has reviewed adverse reaction reporting systems to obtain a better understanding of the safety of antihistamines. Two major sources of data are the adverse reaction files of the Food and Drug Administration and the latest Poison Control Studies of the National Clearinghouse for Poison Control Centers. Since antihistamines have been extensively marketed for nearly 30 years, the Panel believes that a review of adverse reactions reports will serve as an indication of their safety.

It should be emphasized that these information sources are not entirely accurate nor do they necessarily give a valid picture of the incidence or prevalence of particular side effects. However, these reporting mechanisms do highlight the types of adverse reactions that can be expected. Where massive overdoses are ingested, such as in suicide attempts, these reports give a clearer picture of an ingredient's toxicological profile, significant elements of which include morbidity levels, toxic reactions which occur at varying dosage levels as well as dosage levels at which reversibility of an ingredient's toxic effects may occur.

The latest "Poison Control Statistics," published by the National Clearinghouse for Poison Control Centers provides the latest published data now available and covers the period from January to December, 1973 (Ref. 2). This publication presents collective toxicity data on household products and medicines from the Nation's 580 Poison Control Centers. This information reflects the treatment or response to each telephone inquiry to the Poison Control Centers concerning a poisoning or accidental ingestion and usually is not verified for accuracy except for the more obvious incongruities. Although only 1973 statistics were reviewed in detail by the Panel, that particular year is considered representative of all the years for which this type data was compiled.

Unlike the Poison Control Center data the adverse reaction data compiled by the Food and Drug Administration are cumulative and represent the total number of reported cases since the reporting system was implemented in 1968. Adverse reactions are reported to the agency in a variety of ways and at various levels of sophistication. These sources include hospitals, physicians, pharmaceutical manufacturers, consumers, or Food and Drug Administration personnel who often obtained these reports from consumers and physicians. While some of the data are verified for accuracy, they are often incomplete. Data are reported as having one of four causal relationships: directly related, probably related, possibly related and remotely related. For the Panel's purposes, only the adverse reactions which are directly or probably related to drug ingestion are discussed. The Panel recognizes that the statistics generated by the Poison Control Center and the Food and Drug Administration can be misleading and must be carefully used in determining the potential health threat of ingredients to consumers because the extenuating circumstances of each individual case are not represented.

A review of these two sources reveals several variables in the collection and comprehensiveness of the data which must be taken into consideration for a realistic view of the statistics compiled. For example, in the Poison Control Center data, few of the ingestions were of a single chemical entity. Most ingestions were of multi-ingredient products identified by brand name or conversly were ingestion of multiple products. Thus, it is improper to clearly attribute the symptom(s) reported to any one ingredient contained in a product. Further, in some cases no clear delineation of the quantity or number of units of an agent ingested is given. These data were often incomplete and left blank or "unknown" on the document. Of those listing a quantity, several were found to be at normal or subnormal dosage levels with no symptoms exhibited. These cases are included in the Poison Control Statistics as a reported "poisoning" when in fact no "poisoning" occurred. In addition, reported cases of hospitalization allude to symptoms serious enough to require treatment in a hospital, but give no indication whether the patient was seen only at the emergency room or actually admitted for treatment. Many of these same weaknesses and inconsistencies in data collection and assimilation also appear in the compilations from the Food and Drug Administration.

The Panel concludes that summaries of the Poison Control Statistics and the data from the Food and Drug Administration can only be used as an indication of the potential threat posed by OTC products because ingestions of both prescription and OTC products are combined in such statistics.

REFERENCES

(1) Loew, E. R., "Pharmacology of Benadryl and the Specificity of Antihistamine Drugs," *Annals of the New York Academy of Sciences*, 50:1142, 1950.

(2) "Poison Control Statistics, 1973," National Clearinghouse for Poison Control Centers, Bethesda, 1973.

7. *Criteria for classification of antihistamines as Category I.* In evaluating the antihistamines submitted for review, the Panel established the following criteria for classification of an ingredient as safe and effective and not misbranded for use as an antihistamine:

a. *Antihistamine activity.* If an ingredient has been tested in animal models and demonstrated to have antihistamine activity, i.e., in vitro test and in vivo tests (animal challenge with histamine and animal anaphylaxis protection), the findings were used to support a Category I determination.

b. *Animal toxicity.* If an ingredient has been tested in animals and found to have a low order of toxicity, the findings were used to support a Category I determination.

c. *Clinical studies.* If an ingredient has been tested clinically and the studies were determined to be controlled double-blind studies of an adequate design that included an appropriate dosing interval for each age group of patients, the findings were used to support a Category I determination. The Panel has discussed adequate design for clinical testing later in this document. (See part VII. paragraph C. below—Data Required for Evaluation.)

d. *Clinical experience.* If an ingredient has been subjected to uncontrolled clinical trials and has been shown to have sufficiently broad acceptable clinical use, i.e., general use and recognition by the medical community of safety and effectiveness for the treatment of allergic rhinitis, the findings were used to support a Category I determination. The Panel has determined that such clinical use may have been acquired while the ingredient was marketed and available only by prescription but only when used for the treatment of allergic rhinitis similar to that to be encountered with OTC use.

e. *Acceptable side effects.* If an ingredient is shown to have side effects in man for which appropriate labeling can be established, i.e., adequate directions for use and warnings against unsafe use such as "May cause drowsiness", the findings were used to support a Category I determination. In considering the acceptability of these side effects, the Panel questioned whether warnings were sufficient or whether the degree of side effects, and possibility of abuse or misuse under ordinary conditions of use, could be compensated for with adequate labeling. The Panel finds that this is an

especially important consideration for recommended dosages of ingredients higher than those currently available for OTC use, e.g., chlorpheniramine 4 mg or for ingredients previously not available for OTC use, e.g., diphenhydramine.

The Panel has summarized the findings in the following table:

Active ingredients	Antihistamine activity [1]	Animal toxicity [2]	Clinical studies [3]	Clinical experience [4]	Acceptable side effects [5]
Brompheniramine maleate	+	+	+	+	+
Chlorpheniramine Maleate	+	+	+	+	+
Diphenhydramine hydrochloride	+	+	0	+	++
Doxylamine succinate	+	+	+	+	++
Methapyrilene fumarate and hydrochloride.	+	+	0	+	++
Phenindamine tartrate	+	+	0	+	+−
Pheniramine maleate	+	+	0	+	++
Phenyltoloxamine citrate	+	+	0	0	+
Promethazine hydrochloride	+	+	0	+	++
Pyrilamine maleate	+	+	0	+	+
Thenyldiamine hydrochloride	+	+	0	0	0
Thonzylamine hydrochloride	+	+	0	+	+

[1] The (+) symbol indicates that the ingredient showed antihistamine activity in animals.
[2] The (+) symbol indicates that animal studies are available and show low toxicity.
[3] The (+) symbol indicates that controlled double-blind clinical studies of adequate design are available. The (0) symbol indicates that no data are available.
[4] The (+) symbol indicates that adequate clinical experience with the ingredient exists. The (0) symbol indicates that no data are available.
[5] The (+) symbol indicates a positive finding of "drowsiness." The (++) symbol indicates a positive finding of "marked drowsiness." The (+−) symbol indicates a positive finding of either "drowsiness" or "nervousness and insomnia." The (0) symbol indicates that no data are available.

The Panel has determined that if four of the five criteria are satisfied (antihistamine activity, animal toxicity, clinical experience and acceptable side effects), the ingredient may be classified as Category I. The Panel has further determined that the availability of clinical studies is not always required for each ingredient. The Panel has fully discussed these ingredients in the appropriate sections below. (See part VII. paragraph B. below—Categorization of Data.)

8. *Summary.* The antihistamine ingredients as a group are strikingly antihistaminic in animal models. This is their main pharmacologic action and appears to be closely related to their clinical effectiveness. The Panel has found that three of these ingredients, chlorpheniramine, brompheniramine, and doxylamine, have been subjected to controlled clinical studies which support their clinical effectiveness. For most of the remaining ingredients marketed OTC, extensive clinical use over a period exceeding 20 years indicates that these antihistaminic drugs are also effective in treating allergic rhinitis. As a group the antihistamines possess a low order of toxicity which the Panel feels is essential for the use of any ingredient in the OTC market.

B. CATEGORIZATION OF DATA

1. *Category I conditions under which antihistamine ingredients are generally recognized as safe and effective and are not misbranded.*

Category I Active Ingredients

The Panel has classified the following antihistamine active ingredients as generally recognized as safe and effective and not misbranded:

Brompheniramine maleate
Chlorpheniramine maleate
Diphenhydramine hydrochloride
Doxylamine succinate
Methapyrilene preparations: Methapyrilene fumarate, Methapyrilene hydrochloride
Phenindamine tartrate
Pheniramine maleate
Promethazine hydrochloride
Pyrilamine maleate
Thonzylamine hydrochloride

a. *Brompheniramine maleate.* The Panel concludes that brompheniramine maleate is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Studies in animals indicate that brompheniramine maleate has low toxicity (Ref. 1). The chief side effect of brompheniramine is sedation which occurs in about 20 percent or less of patients taking clinically effective doses (Refs. 2 and 3). Also observed is an atropine-like effect (anticholinergic action), which is not pronounced, but might have an adverse effect in patients with narrow angle glaucoma. The drying effect due to atropine-like action has been considered to be disadvantageous in patients with asthma because drying of secretions interferes with their removal from the airway. However, the Panel is unable to find evidence that these possible adverse effects are of clinical significance (Ref. 4).

Recovery from accidental overdosage with brompheniramine indicates that this drug has a wide margin of safety (Ref. 5). An injection of 100 mg caused only dry mouth 8 hours later in a hospitalized patient (Ref. 5). Observations in children indicate a relatively low degree of toxicity for brompheniramine (Ref. 2).

A 6-year-old boy tolerated 8 mg/lb/24 hours orally. A 2-year-old boy received a single oral dose of 60 mg without side effects and a 4-year-old boy received 96 mg in a single dose and subsequently had mild drowsiness. A 2½-year-old boy ingested an estimated twenty-five 12 mg tablets in whom hyperactivity and convulsions occurred followed by gastric lavage 2½ hours later with final recovery (Refs. 1 and 6).

The Panel is aware of a reported case of agranulocytosis following therapy with two antihistaminic drugs, thenalidine tartrate and parabromdylamine maleate (Ref. 7). The incident occurred during 1958 in which a 64-year-old female had taken both drugs. The drug manufacturer of thenalidine tartrate discontinued marketing the ingredient within months of its reported association in the medical literature with agranulocytosis. The other drug, parabromdylamine maleate, is also known as brompheniramine maleate. The patient had taken 4 mg brompheniramine maleate orally 4 times daily concurrently with an antibiotic ointment for the treatment of a pruritic rash. The patient received a total dose of 568 mg brompheniramine maleate over a period of approximately 60 days. The symptoms persisted and the drug was discontinued at which time 25 mg thenalidine tartrate was given orally 4 times daily for an additional period of approximately 60 days for a total dose of 1,850 mg thenalidine maleate prior to hospitalization. The author reporting the case noted that previous investigators had reported three cases of agranulocytosis associated with thenalidine tartrate therapy (Ref. 8). The Panel concludes that the data do not adequately substantiate that brompheniramine maleate was the causative factor in producing the blood dyscrasia. The drug has been extensively marketed and available by prescription for over 15 years with no documented cases of agranulocytosis occurring.

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 600 million dosage units of brompheniramine maleate were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 568 reported cases of suspected poisonings for brompheniramine maleate, 17.1 percent exhibited some symptoms and 5.5 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There was one fatality reported with the drug identified as a contributing cause of death but it was not possible to determine whether the ingestion was accidental or suicidal.

The Panel's review of the data supplied by the Food and Drug Administration showed a total of 47 adverse reaction reports on three marketed products containing brompheniramine since 1968 (Ref. 9). Of the 47, no adverse reactions were listed as being definitely related to ingestion of brompheniramine, 43 were listed as probably caused by ingestion of the drug and 4 were listed as possibly related to its ingestion.

The only other serious adverse reaction, aplastic anemia, was listed as possibly related to brompheniramine ingestion. A review of the source document disclosed few details of the case except that several other drugs were also ingested. The Panel was unable to conclude from the sketchy data whether there was any relationship between ingestion of brompheniramine and the aplastic anemia.

It should be noted that while brompheniramine is currently available only by prescription, the dosage levels are comparable to those that would be available in OTC use. Therefore, the safety considerations presented to the Panel for prescription marketing have given a reasonably accurate picture of what to expect from OTC use of this ingredient.

The Panel concludes that brompheniramine maleate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* Studies in animals have shown brompheniramine to have intense antihistaminic activity and to protect against anaphylaxis (Refs. 1 and 6). In addition to its demonstrated effectiveness as an antihistamine and protection against anaphylaxis in animals, brompheniramine has been shown in double-blind studies in humans to be effective in suppressing the symptoms of allergic rhinitis in doses of 4 mg or more given at 4 to 6 hour intervals (Refs. 10 through 12).

Available evidence indicates that brompheniramine has about the same effectiveness on a mg for mg basis as chlorpheniramine (Ref. 13).

In studies of the treatment of perennial rhinitis, efficacy was reported in 23 children ages 2 months to 2 years at a dosage of 0.2 mg to 0.5 mg/lb in 24 hours divided into 3 doses (Ref. 2). Likewise, 0.2 mg/lb in 24 hours was reported as effective in 28 children ages 2 to 6 years and 0.15 mg/lb in 24 hours in 16 children ages 6 to 14 years. Most of these patients had received other antihistamines without benefit. In addition to treatment with brompheniramine, all had been instructed in environmental control measures and many were receiving injections of allergenic extracts. The contribution made by these measures to the reported benefit cannot be assessed. There were no controlled groups although the statement is made that the patients were selected by "alternate allocation," the meaning of which is unclear. The statement that over three-fourths of the patients had failed to obtain benefit from "various other antihistaminic agents" is surprising in the light of what is known today about the efficacy of the antihistaminic drugs in rhinitis. Therefore, the Panel concludes that evidence of effectiveness for children is insufficient.

The Panel concludes that brompheniramine maleate 4 mg is the minimum effective OTC dosage for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 4 mg every 4 to 6 hours not to exceed 24 mg in 24 hours. Children 6 to under 12 years oral dosage is 2 mg every 4 to 6 hours not to exceed 12 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII. paragraph B.1. below—Catagory I Labeling.) In addition, the Panel recommends the following specific labeling: *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 1 mg every 4 to 6 hours not to exceed 6 mg in 24 hours.

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b. *Chlorpheniramine maleate.* The Panel concludes that chlorpheniramine maleate is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* The chief side effect of chlorpheniramine is sedation which occurs in about 10 to 20 percent of persons taking clinically effective doses. The drug also has a mild atropine-like effect (anticholinergic action) in some patients. This effect might have an adverse effect in patients with narrow angle glaucoma. Likewise, a drying effect has been considered to be a disadvantage in patients with asthma because drying of secretions interferes with their removal from the airways. Data supporting these potentially adverse effects in glaucoma and asthma are not available. Overdosage with chlorpheniramine has been relatively well tolerated. Adults receiving 1.5 gm orally in 69 hours and 200 mg in a single intramuscular dose recovered from the induced side effects without incident (Ref. 1) as did a 4-year-old boy who received 175 mg orally in 3½ hours (Ref. 2).

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 2 billion dosage units of chlorpheniramine maleate were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 1,609 reported suspected poisonings for chlorpheniramine maleate 15.8 percent exhibited some symptoms and 5.3 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug.

The Panel's review of the data supplied by the Food and Drug Administration disclosed a total of 14 adverse reaction reports on chlorpheniramine since 1968 (Ref. 3). Of the 14 reports, no adverse reactions were listed as being definitely related to ingestion of chlorpheniramine, three were listed as probably caused by this drug's ingestion, five were listed as possibly related to its ingestion and six were listed as remotely related to ingestion of this drug.

It should be noted that chlorpheniramine is available by prescription at the 4 mg dosage level and OTC at the 2 mg dosage level. However, the safety picture presented by the prescription dosage level has given the Panel a reasonably accurate idea of what to expect from OTC marketing of the 4 mg dosage level.

The Panel concludes that chlorpheniramine maleate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* Chlorpheniramine has been demonstrated to be effective in animal challenge tests with histamine in anaphylaxis protection (Ref. 4). In addition, its effectiveness in doses of 4 to 8 mg 4 times daily in the treatment of allergic rhinitis is described in a number of articles and uncontrolled studies and is supported by controlled studies (Refs. 5 through 8).

In a double-blind controlled study of the effectiveness of doxylamine succinate, chlorpheniramine was included as a standard of effectiveness. In this study 7.5 mg and 12.5 mg doxylamine were compared with chlorpheniramine 4 mg and a placebo, all given 4 times daily. Each group contained approximately 40 patients and the study extended for 1½ days. Chlorpheniramine and both dosages of doxylamine gave relief of pollen-induced symptoms of allergic rhinitis as compared with the placebo. The effectiveness of chlorpheniramine 4 mg was not significantly different from 7.5 or 12.5 mg doxylamine. In this study measurements of resistance to nasal air flow were made and failed to show any effect of the antihistamine preparations as compared with the placebo (Ref. 9). Other studies corroborate this finding. Using measurements of resistance to airflow in the nose, a well-controlled study

to determine the effect of chlorpheniramine given in an oral dose of 4 mg on relief of nasal obstruction gave no objective evidence of any effect over a period of 4 hours (Ref. 10). There was a significant decrease in resistance to flow when pseudoephedrine was given in a dose of 30 mg, indicating that the method was capable of revealing therapeutic effect. Likewise, a study submitted in an OTC Volume showed increased nasal obstruction in patients with nonallergic acute rhinitis after 8 mg chlorpheniramine in sustained action form (Ref. 11). Both of these studies were done in patients without evidence of allergy. These studies indicate that chlorpheniramine does not relieve and indeed, may aggravate nasal obstruction.

Only one study (Ref. 5) appears to have been done using a 2 mg dose, which is commonly used in OTC preparations, demonstrating effectiveness. The Panel concludes that chlorpheniramine maleate has not been shown to be effective for adults at a dose less than 4 mg.

The Panel concludes that chlorpheniramine maleate 4 mg is the minimum effective OTC dosage for adults for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 4 mg every 4 to 6 hours not to exceed 24 mg in 24 hours. Children 6 to under 12 years oral dosage is 2 mg every 4 to 6 hours not to exceed 12 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII. paragraph B.1. below—Category I Labeling.) In addition the Panel recommends the following specific labeling: *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 1 mg every 4 to 6 hours not to exceed 6 mg in 24 hours.

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c. *Diphenhydramine hydrochloride.* The Panel concludes that diphenhydramine hydrochloride is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Diphenhydramine has a low order of toxicity in laboratory animals (Ref. 1). Its first clinical use was in 1946. Since then it has been used widely for treatment of such common conditions as allergic rhinitis, sundry rashes, the "common cold", and has also been used as a sedative. With the exception of sedation, adverse effects have been rare and the drug is considered safe. The Panel has also reviewed the side effects and toxicity of diphenhydramine when used as an antitussive and finds it to be safe when used at the same dosage level and regimen. That safety discussion is included elsewhere in this document. See part III. paragraph B.1.c. above—Diphenhydramine hydrochloride.)

In a double-blind study in 20 males (Ref. 2) there was no evidence of interference with tests for memory, rotary pursuit, or reaction time at a dose of 12.5 mg or 25 mg. These doses are below that recommended for adults on the treatment of allergic rhinitis. Clinical experience indicates that about 50 percent of persons have drowsiness as a side effect when 50 mg is given (Refs. 3 and 4). In some individuals, this occurs to a degree which would probably impair competence in driving a car or operating machinery. An atropine-like effect is also frequently described by patients as a drying sensation of the mouth and nose.

Many toxicologic studies have been carried out on diphenhydramine hydrochloride. Unpublished animal studies performed with mice demonstrated the LD_{50} to be 145 mg/kg and 263.0 mg/kg (Refs. 5 through 7). In rats, the LD_{50} was found to be 520 mg/kg and 549.5 mg/kg. The results of these studies are very similar when different animal strains, times when the studies were run, and variations inherent under different laboratory conditions are considered (Ref. 5). Diphenhydramine hydrochloride was demonstrated to have low toxicity in all three studies. Based upon these studies the usual adult human oral dosage level of 50 mg or 0.7 mg/kg 3 to 4 times daily is $\frac{1}{200}$th of the oral LD_{50} of diphenhydramine hydrochloride in mice (the LD_{50} is equivalent to at least 200 times the therapeutic dose in man) and $\frac{1}{700}$th the LD_{50} in rats (the LD_{50} is equivalent to at least 700 times the therapeutic dose in man) (Ref. 5).

In chronic toxicity studies dogs were given diphenhydramine hydrochloride at dosage levels of 10, 25, 40 and 60 mg/kg/day for periods up to 6 months. There were no gross microscopic pathologic changes attributable to diphenhydramine hydrochloride (Ref. 5).

Toxic psychoses from overdoses of diphenhydramine have occurred. A case of schizophrenic-like behavior was described by Nigro (Ref. 8). Possibly the earliest suicide was that reported by Duerfeldt in 1947 (Ref. 9).

Wyngaarden and Seevers also found that very high doses of diphenhydramine in infants may cause excitement and convulsions. They reviewed three cases in children under 3 years of age (2½, 1⅔, and 1½ years of age) who had taken 850 mg, 800 mg and 150 to 250 mg of diphenhydramine respectively with all doses resulting in convulsions (Ref. 10). In another case, a 32-month-old baby swallowed 9 capsules (450 mg) of diphenhydramine, after which a state of excitation was observed. Phenobarbital was prescribed, and the next day, the baby was normal (Ref. 10).

They also reviewed a group of adults ranging from 18 to 72 years, who sustained nonfatal convulsions, excitation, toxic psychosis, coma, petit mal, or somnolence (Ref. 10).

One case involved a 72-year-old asthmatic man, weighing 145 pounds who ingested 2,500 mg (50 capsules) of diphenhydramine hydrochloride. He fell into a deep sleep. Approximately 16 hours later, he awoke, feeling well. He had received no medication for this somnolence. In other cases dealing with adult fatalities, Wyngaarden and Seevers found that the ability to withstand large overdoses appears to increase with age, and the older the patient, the more the toxic manifestation shifts from that of central nervous system stimulation to that of depression. But it was also seen that a 47-year-old severely asthmatic woman died in depression after ingesting only 200 mg of diphenhydramine hydrochloride. However, the death cannot be unequivocally attributed to diphenhydramine since the shock-like state observed could well have been a complication of the disease itself and could easily have been influenced by other depressant medicaments that were given (Ref. 9).

The Panel considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 187.4 million dosage units of diphenhydramine hydrochloride were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 334 reported suspected poisonings for diphenhydramine hydrochloride, 37.4 percent exhibited some symptoms and 16.5 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were two fatalities reported with the drug identified as a contributing cause of death.

The Panel's review of the data supplied by the Food and Drug Administration disclosed a total of 178 adverse reaction reports on diphenhydramine since 1968 (Ref. 11). Of those 178 reports, nine were listed as definitely related to diphenhydramine ingestion, 95 were listed as probably caused by the drug's ingestion, 58 were listed as possibly related to its ingestion and 16 were listed as remotely related to diphenhydramine ingestion.

A 69-year-old female who had a history of serious medical problems and

drug ingestion was diagnosed to have agranulocytosis. Three days after termination of pentazocine lactate by injection and 1 day after termination of diphenhydramine therapy, her white blood cell count progressively climbed to normal values (Ref. 11).

The Panel is aware that recently there was some concern expressed about the potential for misuse and abuse of diphenhydramine. This concern was contained in the statement of the Commissioner of Food and Drugs, which was included in the preamble to the report of the OTC Advisory Panel on Sedatives, Tranquilizers and Sleep Aid Drug Products and published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292). This Panel will not attempt to comment on the findings of the other Panel or on the societal impact or abuse potential of diphenhydramine when used as an OTC nighttime sleep-aid. However, after a review of all the available data, the Panel concluded that diphenhydramine, as well as the other antihistamines reviewed, have a very low abuse potential and that there is little if any evidence of tolerance or habituation. However, the Panel does recognize that doses of diphenhydramine higher than those recommended for OTC use are likely to result in some side effects but that these side effects are sufficient to discourage abuse or misuse. In addition, the two pharmacologic groups for which this Panel is recommending diphenhydramine for OTC use, i.e., as an antitussive and as an antihistamine, are not recognized as being abusable by the drug abusing subculture. It should also be noted that diphenhydramine is available without a prescription for use as an antihistamine in Canada, the United Kingdom, and many other industrialized countries of the world. The Panel was unable to determine that significant abuse of this ingredient was a problem in any of these countries.

The Panel notes that the dosage levels of diphenhydramine currently available by prescription are comparable to those that would be available for OTC use. Therefore, the safety considerations presented to the Panel for prescription marketing have given a reasonably accurate picture of what to expect from OTC use of this ingredient.

The Panel concludes that diphenhydramine hydrochloride is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* In animal tests, diphenhydramine has an intense antihistamine action both in vitro (Refs. 1 and 12) and in vivo (Refs. 1 and 13). The drug gives protection to guinea pigs against anaphylactic shock (Ref. 13).

Diphenhydramine is also effective for the symptomatic treatment of allergic rhinitis. Although no studies with a double-blind control were found, the Panel's opinion concerning effectiveness in the treatment of allergic rhinitis rests on wide usage over a period of 30 years.

A number of uncontrolled clinical studies indicate that the drug is effective in relieving the symptoms of allergic rhinitis (Refs. 14 through 16) and one study also describes reduction of whealing in the skin induced by intracutaneous injection of both histamine and allergic extracts in patients with hay fever (Ref. 17). The Panel has also found the drug to be effective for use as an antitussive, which is discussed elsewhere in this document. (See part III. paragraph B.1.c. above—Diphenhydramine hydrochloride.)

The Panel concludes that diphenhydramine hydrochloride 25 to 50 mg is an effective OTC dosage range for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 25 to 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 to 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistaminic active ingredients. (See part VII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "May cause marked drowsiness."

(ii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 6.25 to 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours.

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d. *Doxylamine Succinate.* The Panel concludes that doxylamine succinate is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Doxylamine has a low oral toxicity in laboratory animals (LD_{50}: mice 470 mg/kg; rabbits 250 mg/kg) at doses which greatly exceed those required to demonstrate antihistaminic effects (Ref. 1). Brown and Werner found the intravenous LD_{50} to be 49 and 62 mg/kg for rabbits and mice, respectively (Ref. 1). The subcutaneous dose in mice was about 87 percent less toxic than when given intravenously. The oral dose was about 80 percent less toxic than when given in rabbits. The administration of doses of doxylamine succinate as high as 45 mg/kg twice daily for a period of 38 days had no significant effect in rats. Repeated administration of increasing doses from 50 to 150 mg/kg also had no gross effects. However, an increase to 200 mg/kg resulted in a decreased rate of growth in some animals, and an increase up to 400 mg/kg caused lack of appetite and death in one case. Thus, repeated doses resulted in toxicity only when the doses approached acutely lethal ones (Ref. 1). Daily administration of doxylamine to dogs, rats and monkeys in doses of 3 to 7.5 mg/kg for 2 months gave no evidence of accumulation and the drug was well tolerated (Ref. 2).

Clinical experience indicates that the primary side effect in humans is central nervous system depression. Standard scientific tests state that there is a high incidence of sedation at the usual therapeutic dosage of 12.5 to 25 mg up to 4 times daily (Refs. 3 through 7). In one double-blind, placebo controlled study, the hypnotic effectiveness of doxylamine, 25 to 50 mg, was greater than that of 100 mg secobarbital (Ref. 8). Dizziness and nervousness occur less frequently than sedation (Ref. 3).

One study reports that of 118 patients being treated for allergy with doses of

12.5 to 50 mg of doxylamine succinate, side effects were observed in 39 (Ref. 9). Sedation or sleepiness was seen in 36 of these 39 patients or 92 percent. Nervousness was noted in four patients, and vertigo in four others. No serious toxic effects were noted after use of the drug for 6 months. Sheldon et al. (Ref. 10) gave allergic patients 12.5 to 50 mg of doxylamine succinate and found that 57 percent complained of drowsiness. However, there was no apparent correlation, they stated, between the dosage of the drug and drowsiness. Palpitation, irritability, and diarrhea were noted in three patients. There was no evidence of any hepatic, renal or vascular changes. In the study by Ferguson there was no change in pulse, respiration, temperature or blood pressure with high doses of up to 1,600 mg of doxylamine succinate daily by mouth for up to 6 months (Ref. 11). Blood chemistry and organ function tests remained normal. In addition, Ferguson found that there has been no habituation to doxylamine, but he noted a mild degree of tolerance (Ref. 11).

Selzer and Waldman gave chronic psychotic patients doses of doxylamine (unspecified salt) up to 900 mg/day for 3 months in which side effects were virtually nonexistent (Ref. 12).

In a review of antihistaminic drugs, it is reported that 36 percent of 56 patients receiving the drug for treatment of allergic rhinitis had side effects, chiefly drowsiness (Ref. 13).

It appears from some studies that 50 mg and above of doxylamine succinate produces the side effect of sedation which is characteristic of antihistamines (Refs. 9 and 13). However, as stated above, Ferguson (Ref. 11) and Selzer and Waldman (Ref. 12) gave doses up to 900 mg daily in three divided doses with little evidence of drowsiness in the schizophrenic patients. Such apparently contradictory results have not yet been explained.

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 60 million dosage units of doxylamine succinate were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 100 suspected poisonings reported for doxylamine succinate, 32 percent exhibited some symptoms and 5 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug.

The Panel has reviewed and concurs with the statement in the report of the Advisory Review Panel on OTC Sedatives, Tranquilizers and Sleep-Aid Drug Products published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292) "that no literature was found by the Panel concerning poisoning or doses which cause death in humans."

The Panel's review of the data supplied by the Food and Drug Administration disclosed a total of 10 adverse reaction reports on doxylamine succinate since 1968 (Ref. 14). Of the 10 reports none was listed as directly related to ingestion of doxylamine succinate, five were listed as probably caused by this drug's ingestion, three were listed as possibly related to its ingestion and two were listed as remotely related to ingestion of doxylamine succinate.

The Panel concludes that doxylamine succinate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* Doxylamine is highly active in the protection of guinea pigs against the intravenous injection of histamine (Ref. 1). Using ileum strips in vitro, marked antihistaminic action was also demonstrated. The drug was also effective in protecting guinea pigs against anaphylaxis (Ref. 1).

Clinical experience and standard scientific textbooks indicate that doxylamine is an effective antihistamine in dosages of 12.5 to 25 mg up to 4 times daily (Refs. 3, 7, and 15).

Two double-blind clinical trials have demonstrated the effectiveness of doxylamine in a dosage of 12.5 and 25 mg up to 4 times daily in the treatment of hay fever (Refs. 15 and 16). In these studies, subjective evaluations by patients and physicians were logged and analyzed.

In a third well-designed study, doxylamine was given in a dose of 7.5 mg to one group and in a dose of 12.5 mg to a second group and a placebo to a third group, all with allergic rhinitis caused by pollen. The preparations were administered 4 times a day as required for 6 days with double-blind control. There were 40 to 45 patients in each group. Both the 7.5 mg and 12.5 mg dosages gave significant relief of symptoms as compared with the placebo, with the effectiveness of 12.5 mg exceeding that of 7.5 mg (Ref. 17). The incidence of drowsiness in both the 7.5 mg and 12.5 mg groups was not different from placebo.

In a fourth well-designed study with double-blind control, 7.5 and 12.5 mg doxylamine were compared with chlorpheniramine 4 mg and a placebo, all given 4 times daily. Each group contained approximately 40 patients and the study extended for 1½ days. Chlorpheniramine and both dosages of doxylamine gave relief of pollen-induced symptoms of allergic rhinitis as compared with the placebo. The effectiveness of chlorpheniramine 4 mg was not significantly different from either 7.5 or 12.5 mg doxylamine. In this study, measurements of resistance to nasal air flow were made and failed to show any effect of the antihistamine preparations as compared with the placebo (Ref. 17). One study ranked doxylamine 8th in a series of 13 antihistamines tested for antihistamine activity in man (histamine wheal test) (Ref. 18). Doxylamine has also been described as being slightly "less potent" than promethazine but having a longer duration of action (Ref. 5). An effective dosage for children 6 to 12 years of age is 6.25 mg 2 to 4 times daily (Ref. 3) or 2 mg/kg/24 hours of 60 mg/m²/24 hours divided in 4 to 6 doses (Ref. 19).

The Panel concludes that doxylamine succinate 7.5 mg is the minimum effective OTC dosage for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 7.5 to 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 6 to under 12 years oral dosage is 3.75 to 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "May cause marked drowsiness."

(ii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 1.9 to 3.125 mg every 4 to 6 hours not to exceed 18.75 mg in 24 hours.

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e. *Methapyrilene preparations (methapyrilene fumarate, methapyrilene hydrochloride)*. The Panel concludes that methapyrilene fumarate and methapyriline hydrochloride are safe and effective for OTC use as antihistamines in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* In animal studies, methapyrilene appears to have a low order of toxicity in laboratory animals as compared with other common antihistaminics (Refs. 1 and 2). From the results of human studies, methapyrilene appears to be safe at the recommended dosage (Ref. 3). Specifically, in the Friedlaender and Friedlaender study (Ref. 4) of 117 patients, one or more side effects, usually mild in nature, were encountered in approximately 25 percent of the patients receiving methapyrilene hydrochloride. These occurred most often when doses of 100 mg were administered but usually abated after the initial treatment and seldom affected the continued use of the drug. In most instances, a reduction in dosage to 50 mg obviated the side effects while not modifying the effectiveness. Drowsiness, the most common side effect, occurred in 13 patients. Vertigo, headache, nausea and vomiting, diarrhea and excessive dryness of mouth were next in order of frequency. No serious toxic effect was observed in any patients in this group receiving a daily dose of 200 to 300 mg (50 mg every 4 to 6 hours) (Ref. 4).

In another study, Peirce and Mothersill studied 77 patients and reported that five patients who had been treated with methapyrilene hydrochloride in daily amounts of 100 to 200 mg showed minor side effects but no toxic symptoms (Ref. 5). Rarely did side effects interfere with the patient's ability to continue the administration of the drug. In some cases, lowering the dosage obviated the side effects without significantly altering the therapeutic effectiveness of the drug. Peirce and Mothersill concluded that, ordinarily, 200 mg could be taken daily with "no discomfort" (Ref. 5).

Douglas stated that methapyrilene hydrochloride has been found to have low to intermediate activity for sedation, and its action is less pronounced than that of other antihistamines in therapeutic doses, particularly diphenhydramine (Ref. 3). Occasionally, the anticholinergic action of antihistamines generally may predominate and methapyrilene may cause excitation that results in insomnia, tremors, nervousness, irritability, and palpitation. Dryness of mouth, blurred vision, urinary retention, tachycardia, and constipation may also occur, but these reactions are rare unless large doses are used (Ref. 3). This same view of the toxicity of methapyrilene also appears in several other standard scientific texts (AMA Drug Evaluation, and New and Nonofficial Drugs) (Refs. 6 and 7). However, AMA Drug Evaluation also states that convulsions have been reported in patients with focal lesions of the cerebral cortex and in individuals who have ingested toxic doses (Refs. 6 and 7).

In a study of three patients receiving 400 mg a day for 8 to 10 weeks, no change in blood or urine constituents was observed (Ref. 4). An accidental overdose of 800 mg methapyrilene in a 20-month-old infant resulted in cyanosis, loss of consciousness, convulsions, and cardiorespiratory depression with eventual recovery (Ref. 8). An unusual case of fever, rigor, vomiting, and general malaise with recovery after 3 days is also described (Ref. 9). The symptoms recurred after challenge with methapyrilene 2 weeks after the initial attack. An 18-year-old man who became stuporous after ingestion of an unknown quantity of methapyrilene recovered (Ref. 10).

Methapyrilene fatalities have included a 16-month-old girl who developed hyperpyrexia, cerebral edema, upper nephron nephrosis and uremia (Ref. 11), an adult suicide who died in convulsions after ingestion of methapyrilene (Ref. 12), and two other adults who were found dead (Refs. 13 and 14). Nonfatal cases include two adults (Ref. 15) manifesting convulsions, and two other adults in coma (Ref. 16).

The panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which 543 million dosage units of methapyrilene were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 168 suspected poisonings reported for methapyrilene fumarate or methapyrilene hydrochloride, 11.9 percent exhibited some symptoms and 5.9 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug.

The Panel's review of the data supplied by the Food and Drug Administration showed a total of one adverse reaction report on methapyrilene since 1968 (Ref. 17).

The Panel concludes that methapyrilene fumerate and methapyrilene hydrochloride are safe for OTC use as antihistamines in the dosage ranges described below.

(2) *Effectiveness.* Tests in animal models have demonstrated methapyrilene's specific antihistamine activity. Methapyrilene prevents histamine-induced contraction of the guinea pig ileum and protects sensitized guinea pigs from anaphylactic shock when challenged with an antigen (Refs. 2 and 18).

No double-blind human studies using methapyrilene alone were found. Uncontrolled studies of methapyrilene reported that 63 to 79 percent of patients suffering from hives or hay fever were relieved following administration of the drug (Refs. 4, 5, 15, 18, and 19). In the Friedlaender study, approximately 75 percent of the 40 patients suffering from acute seasonal hay fever obtained some benefit from methapyrilene fumarate or methapyrilene hydrochloride, although the relief of the symptoms was seldom complete. This study utilized 100 mg doses in adults, administered 4 times daily, after meals and at bedtime (Ref. 20).

The Peirce and Mothersill study found that 75 patients received methapyrilene hydrochloride for periods varying from 1 day to 3 months (Ref. 5). The medication exhibited its greatest effectiveness in acute skin rash due to drug and food allergy, watery eyes and runny nose due to pollen sensitivity, and histamine induced headaches. They found that the effective dosage ranged from 50 to 400 mg daily. The average maintenance dose for all cases was between 150 to 200 mg daily (Ref. 5).

In the Feinberg and Bernstein study of 112 patients with allergic rhinitis (seasonal as well as that due to the pollen of trees, grasses and weeds, and to the spores of molds), 79 patients or 70 percent benefited from methapyrilene hydrochloride. Of 95 patients with vasomotor rhinitis (nonseasonal hay fever) 44 patients or 46 percent received some measure of relief (Ref. 19). The symptoms of asthma were not appreciably altered in 30 patients although the preasthmatic, spasmodic cough was decidedly helped in 6 out of 9 patients. The subjective symptoms of skin rash were helped in 4 of 12 patients. In 13 patients with atopic dermatitis (skin rash), 8 obtained considerable relief from itching. The average dose of methapyrilene hydrochloride in the Feinberg-Bernstein study was 50 mg orally, 1 to 4 times daily (Ref. 19). A controlled study of 236 patients receiving methapyrilene and 203 receiving powdered starch presented no evidence that methapyrilene aborted or ameliorated colds (Ref. 20).

The Panel concludes that methapyrilene fumarate 50 mg and methapyrilene hydrochloride 50 mg are the minimum effective OTC dosages for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 6 to under 12 years oral dosage is 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "May cause marked drowsiness."

(ii) *Professional labeling.* The Panel recommends that labeling provided to health professionals, but not to the general public may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours.

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f. *Phenindamine tartrate.* The Panel concludes that phenindamine tartrate is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Acute toxicity studies in guinea pigs indicated an LD_{50} value of 125 mg intraperitoneally which is approximately the same as the intraperitoneal LD_{50} value for diphenhydramine. Daily doses of 100 mg for 5 months or of 200 mg for 6 months were reported to have no adverse effects on the weight, blood formation, blood glucose and non protein nitrogen of dogs. No histopathological changes were found (Refs. 1 and 2).

In 136 healthy subjects ingesting 75 to 600 mg phenindamine daily for 7 to 31 days, toxicity studies revealed no abnormality of hemoglobin, red cell count or white cell count, urinalysis, blood pressure, electrocardiogram, gastric acidity, glucose tolerance, pulse rate, basal metabolic rate or blood chemistry (Ref. 3). In 15 healthy volunteers receiving 50 mg or more daily for 6 months, the blood and urine remained normal (Ref. 4).

In 280 patients receiving 25 to 150 mg daily (adults averaging 75 mg; children 30 mg daily), there were side effects in 27 percent (Ref. 1). In more than 1,000 subjects side effects were frequent but mild and were directly related to dosage. At 75 mg daily, 15 percent of the subjects developed side effects. At 150 mg daily, 25 percent of 380 patients developed side effects. At 300 mg daily, 50 percent of the patients suffered side reactions, and many discontinued the drug. Receiving a dose of 600 mg daily for 7 days, 75 percent of the patients developed side effects (Refs. 3 and 5). Side effects included insomnia, stimulation, nervousness, dryness of mouth, and drowsiness (Refs. 1 through 6).

The Panel recognizes that phenindamine may produce stimulation in some persons and drowsiness in others (Ref. 7). In one study, stimulation is reported to have occurred in 35 percent of patients (Ref. 4). In a review of clinical studies (Ref. 7) comprising 250 patients with allergic rhinitis, it was reported that 3 percent had drowsiness and 12 percent had stimulation. However, data that would establish the frequency of stimulation or drowsiness among those taking the drug in recommended dosages are inadequate and cannot be used for making phenindamine an exception with respect to a warning regarding the occurrence of drowsiness as a side effect.

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 14 million dosage units were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 118 reported suspected poisonings for phenidamine tartrate, 21.2 percent exhibited some symptoms and 10.2 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug.

The Panel's review of the data supplied by the Food and Drug Administration disclosed no adverse reaction reports on phenindamine tartrate since 1968 (Ref. 8).

The Panel concludes that phenindamine tartrate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* The Panel concludes on the basis of clinical reports that phenindamine tartrate is effective for OTC use in the treatment of the symptoms of allergic rhinitis (Refs. 2, 3 and 6).

Phenindamine tartrate demonstrated antihistaminic activity in animals. It could protect guinea pigs against lethal doses of histamine. The histamine-induced contraction of guinea pig intestinal strips in vitro was inhibited by phenindamine. The drug also had a protective action in guinea pigs against fatal anaphylactic shock produced by horse serum sensitization (Refs. 1 and 2).

Clinical trials have also shown the effectiveness of phenindamine tartrate as an antihistamine in man. A dose of 200 mg of phenindamine inhibited the wheals and flares produced in ragweed-sensitive patients after they were skin-tested with ragweed or histamine (Ref. 2).

In a subjective, uncontrolled clinical evaluation of phenindamine in 389 patients with allergic conditions such as hay fever, allergic perennial rhinitis, bronchial asthma, atopic dermatitis, contact dermatitis, urticaria and angioneurotic edema, and migraine, a dose of 25 mg every 4 hours was given orally (Ref. 2). Of the 180 patients in the study with hay fever who took the drug during the hay fever season, 44 percent reported complete relief, 32 percent reported moderate relief, 14 percent had slight relief and 10 percent reported no relief. In the 71 patients with allergic perennial rhinitis, 35 percent had complete relief, 39 percent moderate relief, 9 percent slight relief and 17 percent had no relief. The relief from a dose of 25 mg lasted approximately 2 to 5 hours. Of the 389 patients, 23 percent had side reactions such as nervousness, palpitations, nausea, vomiting, insomnia, drowsiness, headache, constipation, etc. No appreciable change was seen in blood pressure or electrocardiogram.

In another report, 78.2 percent of 197 patients with hay fever who were given a daily dose of 25 to 150 mg of phenindamine for an average of 17 days reported fair to excellent relief (Ref. 1). The drug was of benefit to 76.1 percent of the 71 patients with nonseasonal vasomotor rhinitis in this study.

The symptomatic relief of allergic rhinitis by daily doses of 25 to 200 mg of phenindamine was studied in 131 patients. Seventy-five to 100 percent relief was reported by 105 of these patients whose ages ranged from 2 to 70 years. Only 27 of the patients complained of side effects (Ref. 6). In a study of 40 patients with hay fever, a daily dose of 25 to 75 mg gave marked relief to 52.5 percent, moderate relief to 25 percent, slight relief to 15 percent and 7.5 percent had no relief (Ref. 4). Daily doses of 75 to 120 mg phenindamine for 15 to 120 days to 66 hay fever subjects gave complete

relief to 18 percent, partial relief to 62 percent and 20 percent were not helped (Ref. 3). Daily doses of 75 to 250 mg to 25 patients with vasomotor rhinitis brought no relief for 44 percent and complete relief for 20 percent. At 75 mg daily, approximately 15 percent of the patients showed side effects.

Experience has also indicated that the duration of effect of one 25 mg dose is 2 to 10 hours averaging 4 to 5 hours. The onset of action is rapid, occurring within 15 minutes of ingestion (Ref. 1). In one study, 86 percent of 66 patients with hay fever received moderate to complete relief receiving a dosage of 75 to 150 mg daily. In a review of the antihistamine drugs (Ref. 7), 76 percent of 912 patients with allergic rhinitis were benefited.

In one study, moderate to marked relief of hay fever occurred in 78 percent of 40 patients taking 50 mg daily (Ref. 4).

Seventy-eight percent of patients with hay fever noted fair to excellent relief (Ref. 1). A placebo failed to provide relief of the symptoms in these patients.

The Panel concludes that pheninda-mine tartrate 25 mg is the minimum effective OTC dosage for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients (See Part VII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "*Caution:* May cause nervousness and insomnia in some individuals."

(ii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours.

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g. *Pheniramine maleate.* The Panel concludes that pheniramine maleate is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Pheniramine maleate has been shown in animal experiments to possess a high degree of antihistaminic activity and a low order of toxicity (Refs. 1 and 2). Clinical experience has confirmed that pheniramine maleate is safe in the dosage ranges used as an antihistamine. The chief side effect of pheniramine appears to be sedation. It also appears to have a mild atropine-like effect. Since most of the studies have been done with other drugs combined with pheniramine, the action of this drug alone cannot be described with certainty. In one study in which pheniramine alone was given, drowsiness and dryness of the mouth (atropine-like effect) occurred in 11 percent of the subjects (Ref. 3). In a review of clinical studies with the antihistamine drugs (Ref. 4) 29 percent of 49 patients receiving pheniramine maleate 25 mg for allergic rhinitis had side effects, chiefly drowsiness. Among 184 subjects receiving 10 mg pheniramine 4 times daily in the course of a double-blind study of the "common cold," side effects, chiefly drowsiness, did not significantly exceed the side effects in an equal number of subjects receiving a placebo (Ref. 5). There appear to be no reports of accidental overdose. A single case was described in which acute psychosis occurred following treatment for 2 months with pheniramine 25 mg 3 times daily (Ref. 6). Following withdrawal of pheniramine, recovery occurred in 8 days. No definite conclusion could be drawn in this case as to the role played by pheniramine. An atropine-like effect suggests a potential hazard in patients with enlargement of the prostate gland and also narrow angle glaucoma and this effect has also been considered to be disadvantageous in patients with asthma although data supporting this potentially adverse effect are not available.

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 291 million dosage units were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 358 suspected poisonings reported for pheniramine maleate, 20 percent exhibited some symptoms and 1.7 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug identified as a contributing cause of death.

The Panel's review of the data supplied by the Food and Drug Administration disclosed no adverse reaction reports on pheniramine maleate since 1968 (Ref. 7).

The Panel concludes that pheniramine maleate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* Pheniramine maleate has been shown in animal experiments to possess a high degree of antihistaminic activity (Refs. 1 and 2).

There are no well-controlled studies documenting the effectiveness of pheniramine maleate as an antihistamine. In a review of several reports of clinical experience, pheniramine in a dose of 25 mg gave relief of allergic rhinitis in 81 percent of 442 patients (Ref. 4). Likewise the drug gave relief in 66 percent of patients with nonallergic rhinitis (vasomotor rhinitis).

The Panel concludes that pheniramine maleate 12.5 mg is the minimum effective OTC dosage for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 12.5 to 25 mg every 4 or 6 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 6.25 to 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients (See part VII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "May cause marked drowsiness".

(ii) *Professional labeling.* The Panel recommends that labeling provided to health professionals, (but not to the general public), may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 3.125 to 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours.

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h. *Promethazine hydrochloride.* The Panel concludes that promethazine hydrochloride is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Promethazine is well-tolerated by laboratory animals; doses which greatly exceed those giving protection against histamine are well tolerated by guinea pigs (Ref. 1). Like other antihistamine drugs, promethazine may cause drowsiness when taken in clinically effective doses. In a study in which up to 1 gm was administered therapeutically 4 times daily to psychiatric patients, drowsiness occurred as the most important and frequent side effect (Ref. 2). In a suicide attempt a 35-year-old female survived an estimated dose of 1.5 gm, developing coma and clonic contractions (Ref. 3). Another such case had a similar course after the patient consumed 500 mg of promethazine (Ref. 4). Children may be less tolerant of this drug. Seven to 10 hours after a 12-year-old boy ingested 200 mg, he was hospitalized with many symptoms including restlessness, excitation, stupor, fright and hallucinations. Recovery followed in 3 days (Ref. 5).

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 385 million dosage units were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 56 reported suspected poisonings for promethazine, 28.6 percent exhibited some symptoms and 14.3 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug. This relative incidence of adverse reactions is remarkably low in light of the substantial and long use of the drug (4½ billion oral doses have been used since 1951 (Ref. 6)).

The Panel's review of the data supplied by the Food and Drug Administration showed a total of 169 adverse reactions involving marketed products containing promethazine (Ref. 7). Of the 169, 4 adverse reactions were listed as being definitely related to the oral ingestion or injection of promethazine, 105 were listed as probably caused by the drug's use, 49 were listed as possibly related to its use and 11 were listed as remotely related to promethazine.

Of particular concern are blood dyscrasias which have been reportedly associated with the drug. A total of five adverse experience reports have remotely related blood dyscrasias to promethazine. Analysis of the experience reports indicates that these dyscrasias are not attributable to promethazine. One case of agranulocytosis is reported to have occurred in a patient who was receiving promethazine and methaqualone. The patient's white blood cell count and the neutrophils began to increase and returned to normal 3 days after methaqualone was discontinued. Agranulocytosis was reported in another patient receiving large doses of two antibiotics intravenously who was also receiving oral promethazine. Additional drugs in the regimen included a thyroid derivative and tetracycline prior to the other medications. This blood dyscrasia may well be attributed to the two antibiotics, methacillin and/or cephalothin, both of which are known to cause agranulocytosis. A case of thromocytopenia was reported in a 2-year-old child who developed symptoms of an upper respiratory infection with fever and cough. The patient was treated with aspirin, a product containing triprolidine hydrochloride and pseudoephedrine, and promethazine syrup with dextromethorphan. The attending physician believed that the thromocytopenia was caused by the basic disease process and not by the medications. Leukopenia and thrombocytopenia was reported in a patient receiving promethazine but there are no data provided on the patient's disease state or concomitant drug therapy. On the basis of this limited data it is not possible to determine the cause and effect relationship between promethazine and the blood dyscrasias. Another patient, an 88-year-old male, with an upper respiratory infection who was receiving promethazine, tetracycline and propoxyphene reportedly had hypoplastic anemia secondary to drug reaction. Again, no information on drug dosages or final diagnosis was available and promethazine cannot be determined to cause the hypoplastic anemia.

A further review of adverse reaction reports from the Boston Collaborative Drug Surveillance Program and the University of Florida adverse reaction study shows a low incidence (5.2 percent and 7.1 percent, respectively) of adverse reactions (Ref. 8). The most frequently occurring reactions were drowsiness and confusion or disorientation. In contrast to other phenothiazine derivatives, promethazine showed few incidences of extrapyramidal syndrome (1 of 2,468 patients followed in the studies who received promethazine) and hypotension (3 of 2,468 patients followed in the studies who received promethazine).

Clinical studies (Refs. 1, 9, 10, and 11) indicate that the drug is safe in a dosage effective in allergic rhinitis and authorities in the field of clinical allergy concur (Refs. 12 and 13).

The Panel is aware of the current package insert labeling for promethazine which warns against various possible adverse reactions. These adverse effects are those usually associated with phenothiazine derivatives and clinical experience generally supports their occurrence with most other phenothiazine compounds. According to one authority, jaundice, excessive hypotension or hematopoietic damage have not been reported (Ref. 13). After analysis of published research studies and adverse experience reports on promethazine, however, the Panel concluded that promethazine does not cause the wide range of serious or potentially toxic effects characterizing other members of the chemical class of phenothiazines.

It should be noted that while promethazine is currently available only by prescription, the dosage levels are comparable to those that would be available in OTC use. Therefore, the safety considerations presented to the Panel for prescription marketing have given a reasonably accurate picture of what to expect from OTC use of this ingredient.

The Panel concludes that promethazine hydrochloride is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* In animal studies, promethazine is highly effective in protecting guinea pigs against histamine and the drug is also effective in protecting guinea pigs against anaphylaxis (Ref. 13). Promethazine appears to share with other antihistamine drugs the capacity to suppress rhinorrhea, sneezing and itching but differs from most other antihistamine drugs under consideration in having a longer duration of action. However, no controlled clinical trials appear to have been done to test the effectiveness of promethazine in allergic rhinitis nor in the "common cold". A number of uncontrolled studies indicate that promethazine is effective in the treatment of allergic rhinitis in a dose of 12.5 to 25 mg (Refs. 1, 7, 10, and 13). Based on clinical experience and the data available, the Panel concludes that promethazine is effective when taken in the recommended dosage.

The Panel concludes that promethazine hydrochloride 6.25 mg is the minimum effective OTC dosage for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 6.25 to 12.5 mg every 8 to 12 hours not to exceed 37.5 mg in 24 hours. Children 6 to under 12 years oral dosage is 3.125 to 6.25 mg every 8 to 12 hours not to exceed 18.75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients (See part VII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "May cause marked drowsiness."

(ii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 1.56 to 3.125 mg every 8 to 12 hours not to exceed 9.375 mg in 24 hours.

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i. *Pyrilamine maleate.* The Panel concludes that pyrilamine maleate is safe and effective for OTC use in suppressing symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Chronic animal toxicity studies done by Winter et al. showed no evidence of a cumulative effect (Ref. 1). In that study, pyrilamine maleate had been administered to rats, dogs and monkeys for varying lengths of time up to 6 months. The following doses appeared to be entirely safe: in rats 10 mg/kg 5 times weekly for 6 months and up to 200 mg/kg daily for 32 days; in dogs, 20 mg/kg 5 times weekly for 6 months, and in monkeys, 50 mg/kg daily for 35 days. No toxic signs nor any hematological, biochemical or pathological abnormalities were found in the animals on these doses.

In human studies, pyrilamine has a low order of toxicity. Side effects are not infrequent but are usually mild. They include drowsiness, listlessness, irritability, and anorexia (loss of appetite) (Ref. 2). In a study by Gay et al., only 3 percent of the 147 patients showed any sign of drowsiness and the incidence of loss of appetite, nausea and vomiting occurred in 27 percent of the patients (Ref. 3).

Two fatalities were reported with pyrilamine maleate. One was of a 21-month-old child who had ingested 600 mg and died 2¾ hours after ingestion, exhibiting a post-convulsive coma. The other fatality was of a 2-year-old child that had ingested 1,400 mg and died during convulsions 4 hours after ingestion (Ref. 4).

The Panel's review of the data supplied by the Food and Drug Administration disclosed a total of two adverse reaction reports on pyrilamine since 1968 (Ref. 5). Both of the adverse reactions were miner and neither was listed as directly related or probably caused by the ingestion of pyrilamine.

The Panel has also considered the most recent data available from the records compiled from Poison Control Centers. (See part VII. paragraph A.6. above—Human toxicity.) Of the 358 suspected poisonings reported for pyrilamine maleate, 18.7 percent exhibited symptoms and 1.7 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug.

The Panel's review of the data supplied by the Food and Drug Administration showed a total of only two adverse reaction reports on pyrilamine since 1968 (Ref. 5). Of the two reports, no adverse reactions were listed as being definitely related to ingestion of pyrilamine; both were listed as possibly related to its ingestion.

The Panel concludes that pyrilamine maleate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* In vitro and in vivo animal studies indicate that pyrilamine has an intense antihistamine action (Ref. 6) and that the drug has protective activity against histamine and anaphylaxis in the guinea pig (Ref. 7). Pyrilamine and diphenhydramine were equally effective in protecting against anaphylaxis and in preventing histamine-induced contractions of sensitized guinea pig ileum. Winter found in his animal studies that 0.01 mg/kg of pyrilamine protected 100 percent of 19 guinea pigs against a lethal dose of histamine (0.5 mg/kg) for 2 hours (Ref. 1). Gay et al. used the same dose and 91 percent of the guinea pigs were protected for 2 hours (Ref. 3). In this same study, 80 percent of 10 guinea pigs pretreated with 0.1 mg/kg of pyrilamine survived. The pharmacological effects and the histamine antagonism of pyrilamine are comparable to those of chlorpheniramine and similar to those of the other antihistamines (Refs. 1, 6, and 7).

In an uncontrolled study of several antihistaminic drugs including pyrilamine (Ref. 3), this drug was given to 102 patients with allergic rhinitis of whom 70 percent were improved. Two other comparative uncontrolled studies gave similar findings (Refs. 8 and 9) and in a review of the antihistaminic drugs, 66 percent of 604 patients with allergic rhinitis usually receiving a dose of 50 mg were benefited (Ref. 10).

The Panel concludes that pyrilamine maleate 25 to 50 mg is an effective OTC dosage range for the relief of the symtoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 25 to 50 mg every 6 to 8 hours not to exceed 200 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 to 25 mg every 6 to 8 hours not to exceed 100 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamines. (See part VII. paragraph B.1. below—Category I Labeling). In addition, the Panel recommends the following specific labeling: *Professional labeling:* The Panel recommends that the labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 6.25 to 12.5 mg every 6 to 8 hours not to exceed 50 mg in 24 hours.

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j. *Thonzylamine hydrochloride.* The Panel concludes that thonzylamine hydrochloride is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Thonzylamine hydrochloride has been shown in animal experiments to possess antihistaminic activity and a low order of toxicity (Ref. 1). Clinical experience has confirmed that thonzylamine hydrochloride is safe in the dosage ranges used as an antihistamine. Although there are no controlled studies using thonzylamine, the incidence and degree of side effects appear to be less than with most other antihistamines (Refs. 2 and 3). In one report in which patients with "allergies" received an average dose of 50 to 100 mg orally 2 to 4 times daily, investigators in seven separate studies concurred that

thonzylamine was the "least toxic" of the antihistamines then in general use (Ref. 4). In other studies, the incidence of side effects was also low (Refs. 5 through 9) but the dosage of thonzylamine was generally not specified. Of the entire series of 874 patients, an average of 10.9 percent reported side effects which consisted of slight nervousness, headache, gastric disturbance, drowsiness, and dizziness. Most of these side effects were not significant, but the drug was discontinued in a small number of patients due to headache or gastric disturbance.

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which 80 million dosage units were sold. (See part VII. paragraph A.6. above—Human toxicity.) There were no reported suspected poisonings for thonzylamine hydrochloride.

The Panel's review of the data supplied by the Food and Drug Administration showed no adverse reaction reports on thonzylamine hydrochloride since 1968 (Ref. 10).

The Panel concludes that thonzylamine hydrochloride is safe for OTC use as an antihistamine at the dosage ranges described below.

(2) *Effectiveness.* Thonzylamine hydrochloride, administered orally, is generally recognized as possessing antihistamine properties and providing symptomatic relief in allergic rhinitis. However, there are only uncontrolled studies documenting the effectiveness of thonzylamine hydrochloride as an antihistamine.

Most textbooks and several studies (Refs. 5, 7, and 9) indicate thonzylamine hydrochloride has antihistamine action. In a series of uncontrolled studies, 64 percent of patients with "allergy" benefited from oral doses of 50 to 100 mg thonzylamine hydrochloride 2 to 4 times daily (Ref. 4) while in the other studies, thonzylamine was found to be about as effective as other antihistamine drugs. In a review of the antihistamines, thonzylamine 50 mg was reported to have given benefit in 54 percent of 384 patients with allergic rhinitis (Ref. 11). The studies cited suggest that a recommended dosage of 50 to 100 mg up to 4 times a day is effective.

The Panel concludes that thonzylamine hydrochloride 50 to 100 mg is an effective OTC dosage range for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 50 to 100 mg every 4 to 6 hours not to exceed 600 mg in 24 hours. Children 6 to under 12 years oral dosage is 25 to 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I Labeling for antihistamine active ingredients. (See part VII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 12.5 to 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours.

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Category I Labeling

The Panel recommends the following Category I labeling for antihistamine active ingredients to be generally recognized as safe and effective and not misbranded as well as the specific labeling discussed in the individual ingredient statements:

a. *Indications.* (1) "Alleviates, decreases, or for temporary relief of, running nose, sneezing, itching of the nose or throat and itchy and watery eyes as may occur in allergic rhinitis (such as hay fever)".

(2) "Alleviates, decreases, or for temporary relief of, running nose as may occur in allergic rhinitis (such as hay fever)".

(3) "Alleviates, decreases, or for temporary relief of, sneezing as may occur in allergic rhinitis (such as hay fever)".

(4) "Alleviates, decreases, or for temporary relief of, itching of the nose or throat as may occur in allergic rhinitis (such as hay fever)".

(5) "Alleviates, decreases, or for temporary relief of, itchy and watery eyes as may occur in allergic rhinitis (such as hay fever)".

(6) "Dries running nose as may occur in allergic rhinitis (such as hay fever)".

b. *Warnings.* The drowsiness often produced by the antihistaminic drugs is a potential hazard under circumstances in which alertness is important. Therefore the Panel believes that a warning regarding drowsiness should appear on the label for all products containing antihistamine drugs. The Panel believes it is prudent to regard the atropine-like effects of the antihistamines as a possible hazard in patients with glaucoma and as possibly leading to difficulty in urination in those individuals with prostatic hypertrophy. In asthma, the antihistamines may cause drying of bronchial secretions, making expectoration of the secretions more difficult and thereby increasing obstruction of the airway.

Therefore, the Panel recommends that labeling include the following warnings and cautions: (1) For active ingredients not containing the specific warning "May cause marked drowsiness", the statement "May cause drowsiness" should be used.

(2) "May cause excitability especially in children".

(3) "Do not take this product if you have asthma, glaucoma or difficulty in urination due to enlargement of the prostate gland except under the advice and supervision of a physician".

(4) *"Caution.* Avoid driving a motor vehicle or operating heavy machinery".

(5) *"Caution:* Avoid alcoholic beverages while taking this product".

(6) "Do not give this product to children under 6 years except under the advice and supervision of a physician".

There are insufficient data to establish the safety of OTC preparations containing antihistamines in children under 6 years. Individuals vary widely in the degree to which drowsiness, and less commonly, other adverse effects occur when they are given antihistaminic drugs. For this reason, the frequency and severity of side effects cannot be predicted. Respiration may be depressed and this effect can be serious in infections involving the airway. Parents and others may have difficulty assessing the intensity of induced side effects and children cannot be expected to understand their potential hazards. For these reasons, medical supervision is recommended when children under 6 years are given antihistaminic drugs.

2. *Category II conditions under which antihistamine ingredients are not generally recognized as safe and effective or are misbranded.* The use of antihistamines under the following conditions is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel concludes that the following labeling should be removed from the market until scientific testing supports their use.

Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety and/or effectiveness of the product are unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel has previously discussed such labeling. (See part II. paragraph O. above—CCABA Product Labeling Claims Not Supported by Scientific Evidence.) However, labeling that is de-

scriptive of the product such as its taste or appearance is acceptable.

Unacceptable claims for antihistamines include statements such as the following:

a. *All claims which state or imply a therapeutic action or safety property peculiar to the preparation that cannot be demonstrated in controlled studies.* These include claims such as "specially formulated", "scientifically improved", or "selected", "natural", "extra strength", "teamed components", "superior to ordinary—".

b. *Claims implying a physiological effect which either have no foundation or meaning or will be meaningless or misleading to the public.* Items include: "gets at the root of—"; "fights"; "wakes up"; "recommended by doctors"; "travels through the blood stream".

c. *Claims for relief where time is indeterminate.* Terms include: "fast"; "prompt".

d. *Claims for relief of nasal symptoms (other than running nose, itchy nose, and sneezing).* Terms include: "decreases nasal obstruction"; "decreases nasal congestion"; "relief of stuffy nose (stopped up nose, nasal stuffiness, clogged up nose)".

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel concludes that adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed active ingredients listed below. The Panel believes it reasonable to provide 3 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within 3 years, however, the ingredients listed in this category should no longer be marketed as over-the-counter products. Effectiveness as an antihistamine must be demonstrated by controlled, double-blind studies because of the subjective nature of both the symptoms and the effects of any drug-induced changes.

Category III Active Ingredients

The Panel concludes that the available data are insufficient to permit final classification of the following claimed antihistamine active ingredients:

Phenyltoloxamine citrate
Thenyldiamine hydrochloride (oral)

a. *Phenyltoloxamine citrate.* The Panel concludes that phenyltoloxamine citrate is safe for OTC use but there are insufficient data available regarding its effectiveness to permit final classification as an antihistamine in suppressing the symptons of allergic rhinitis as specified in the proposed dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that phenyltoloxamine citrate is safe in the dose ranges used as an antihistamine. Animal studies have indicated phenyltoloxamine is one of the least toxic antihistamines. As much as 680 mg/kg given orally to rats produced no symptoms. In dogs, 10 mg/kg for 50 days was well tolerated (Ref. 1).

Studies in humans also suggest a low incidence of side effects at a dosage of 100 to 200 mg in 24 hours with moderate drowsiness occurring following dosage in excess of 200 mg in 24 hours (Ref. 2). One reference states that in therapeutic doses, soporific effects occur in less than 7 percent of patients (Ref. 3). A low incidence of side effects, 6.5 percent, was reported in one study in which allergy patients were given 25 or 50 mg 3 or 4 times daily (Ref. 4). In another study (Ref. 5), phenyltoloxamine was given for its "ataraxic" effect in a dosage of 300 mg daily, 100 mg after lunch for daytime sedation and 200 mg at bedtime for nighttime sedation. Side effects were reported to be minimal in this study.

Sainz (Ref. 6) performed a study in 48 patients to determine side effects and toxicity and found that mild drowsiness appeared at oral doses above 200 mg 4 times daily, or with single doses of 400 mg. Ataxia or abnormal reflexes were not noted at oral doses of 400 mg 4 times a day. There were no extrapyramidal symptoms. The EEG was not affected. A slight blood pressure increase was seen and doses higher than 200 mg 4 times daily produced adrenergic stimulation (increased salivation, gastritis, and diarrhea). Heartburn was found in 14 percent of patients taking the drug, and occasionally nausea was seen. No changes were noted in metabolic, nutritional, endocrine, hematologic, urologic or liver function parameters. Sainz concluded that the drug is not only safe but remarkably free from undesirable reactions at oral doses of the dihydrogen citrate salt of phenyltoloxamine at 100 mg (56 mg of the active moiety) 4 times daily.

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which 423 million dosage units were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 90 suspected poisonings reported for phenyltoloxamine citrate, 15.6 percent exhibited some symptoms and 5.6 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug.

The Panel's review of data supplied by the Food and Drug Administration showed only one adverse reaction report on phenyltoloxamine citrate since 1968 (Ref. 7). The adverse reaction was listed as possibly related to abnormal kidney function tests.

The Panel concludes that phenyltoloxamine citrate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of phenyltoloxamine citrate as an antihistamine. Phenyltoloxamine citrate is an antihistamine drug which in animal studies antagonizes most of the pharmacologic actions of histamine (Ref. 1). In clinical use, the drug appears to provide symptomatic relief of allergic symptoms (Refs. 2 and 3), although no controlled studies are available which permit a determination of the minimum effective dosage level.

Cronk and Naumann (Ref. 2) used a dosage of 25 to 50 mg 4 times daily, but reported "relief" only in patients receiving 50 mg 4 times daily. Seyler and Simon (Ref. 4) likewise recommended a dosage of 50 mg 3 or 4 times daily. Thus, clinical experience indicates a daily dosage of 150 to 200 mg.

The Panel concludes that although there are insufficient data to determine that phenyltoloxamine citrate is effective for the relief of the symptoms of allergic rhinitis, 50 mg is the proposed dosage at which this ingredient is most likely effective.

(3) *Proposed dosage.* Adult oral dosage is 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 2 to under 12 years oral dosages are identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 6 to under 12 years oral dosage is 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours; children age 2 to under 6 years oral dosage is 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours.

(5) *Evaluation.* Data to demonstrate effectiveness will be required according to the guidelines set forth below for testing antihistamine drugs. (See part VII. paragraph C. below—Data Required for Evaluation.)

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(7) OTC Volume 040325.

b. *Thenyldiamine hydrochloride (oral).* The Panel concludes that thenyldiamine hydrochloride (oral) is safe for OTC use but there are insufficient data available regarding effectiveness to permit final

classification as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the proposed dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that thenyldiamine hydrochloride (oral) is safe in the dosage ranges used as an antihistamine. The Panel has discussed the topical use of this drug as a nasal decongestant elsewhere in this document. (See part VIII. paragraph B.3.k. below—Thenyldiamine hydrochloride (topical).)

This drug was selected from among several related compounds because of marked antihistaminic and anti-anaphylactic properties and its low toxicity in animals (Refs. 1 and 2). Thenyldiamine is relatively nontoxic in animals. The oral LD_{50} for mice is about 190 mg/kg and for the guinea pig 240 mg/kg. There are no human safety data on the use of thenyldiamine administered orally alone. Data in uncontrolled studies with a combination product containing phenylephrine, acetaminophen and caffeine in addition to thenyldiamine in a dose of 25 to 150 mg daily revealed no significant changes in pulse rate or blood pressure (Refs. 3 and 4). Tabulations of side effects in patients receiving thenyldiamine hydrochloride alone and those receiving the combination formulation are difficult to interpret. The chief side effect appears to be sedation or drowsiness. Dizziness, dryness of the throat, headache, perspiration, and nausea have also been reported (Ref. 1).

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which 2.5 million dosage units were sold. (See part VII. paragraph A.6. above—Human toxicity.) In the one suspected poisoning reported for thenyldiamine hydrochloride, no symptoms were exhibited.

The Panel's review of the data supplied by the Food and Drug Administration showed no adverse reaction reports on thenyldiamine hydrochloride since 1968 (Ref. 5).

The Panel concludes that thenyldiamine hydrochloride is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of thenyldiamine hydrochloride (oral) as an antihistamine and reports of clinical experience are lacking. Thenyldiamine hydrochloride was official in U.S.P. XII. The dose was 15 mg orally. The frequency of treatment was not stated. A secondary reference source indicates the dosage to be 15 to 30 mg (Ref. 6). It appears that effective adult dosage may not be attained by using the commercially available OTC combination products which contain 2.5 to 7.5 mg per dosage unit.

In vitro studies of 0.03 gamma thenyldiamine in a 20 ml bath gave 75 percent inhibition of a standardized contraction produced by 0.3 gamma histamine. The drug compared well with diphenhydramine and pyrilamine as measured by histamine shock in the guinea pig where 1 mg/kg gave complete protection against the LD_{100}. The drug also gave marked protection against anaphylaxis in the guinea pig.

The Panel concludes that although there are insufficient data to determine that thenyldiamine hydrochloride (oral) is effective for the relief of the symptoms of allergic rhinitis, 15 to 30 mg are the proposed dosage at which this ingredient is most likely effective.

(3) *Proposed dosage.* Adult oral dosage is 15 to 30 mg every 4 to 6 hours not to exceed 180 mg in 24 hours. Children 2 to under 12 years oral dosages are identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII. paragraph B.1. above—Category I Labeling.) However, the Panel recommends that the Category I warning pertaining to use in children be revised from 6 years to 12 years with the following specific labeling: (i) *Warning.* "Do not give this product to children under 12 years except under the advice and supervision of a physician". (ii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 6 to under 12 years oral dosage is 7.5 to 15 mg every 4 to 6 hours not to exceed 90 mg in 24 hours; children 2 to under 6 years oral dosage is 3.75 to 7.5 mg every 4 to 6 hours not to exceed 45 mg in 24 hours.

(5) *Evaluation.* Data to demonstrate effectiveness will be required according to the guidelines set forth below for testing antihistamine drugs. (See part VII. paragraph C. below—Data Required for Evaluation.)

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Category III Labeling

The Panel concludes that the available data are insufficient to permit final classification of the labeling claims identified below for antihistamines. Additional data are required to substantiate these claims for OTC antihistamine use: a. The following statements of duration are unacceptable unless documentation can specify the number of hours: "provides hours of relief" "all day" "all night".

b. "Alleviates, decreases or for temporary relief of running nose, sneezing, itching of the nose or throat and itchy and watery eyes as may occur in the common cold".

c. "Alleviates, decreases or for temporary relief of running nose as may occur in the common cold."

d. "Alleviates, decreases or for temporary relief of sneezing as may occur in the common cold".

e. "Alleviates, decreases or for temporary relief of itching of the nose or throat as may occur in the common cold".

f. "Alleviates, decreases or for temporary relief of itchy and watery eyes as may occur in the common cold".

g. "Dries running nose as may occur in the common cold".

h. *Claims that sleep will be facilitated.* Terms include "promotes restful sleep".

C. DATA REQUIRED FOR EVALUATION

The Panel has agreed that the protocols recommended in this document for the studies required to bring a category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved technology in the future.

1. *Principles in the design of an experimental protocol for testing antihistamine drugs in allergic rhinitis.* a. *General principles.* The antihistaminic drugs are indicated for the symptomatic relief of IgE mediated allergic reactions. (See part II paragraph B.1.—Allergy.) When such reactions occur in the upper airway, the symptoms include sneezing, nasal discharge, nasal obstruction and itching of the nose, eyes, throat and ears. Such symptoms may or may not be accompanied by objective manifestations and for this reason, the patients' subjective sensations must be relied upon in the assessment of drug action. However, observations on the degree of edema of the nasal mucus membrane, the quantity of nasal discharge and the degree of injection of the sclerae may be helpful. The action of this group of drugs is limited to a few hours so that reepated doses at regular intervals are required for a sustained effect. All the antihistamines have side effects which again are subjective and have virtually no objective counterpart. Because of the subjective nature of both the symptoms and the effect of any drug-induced change, double-blind experimental control is especially important in the assessment of antihistaminic drugs.

Considerable experience in assessing therapy for allergic rhinitis caused by pollen (hay fever) has accumulated in the past 15 or more years in the course of efforts to determine the effectiveness of injection therapy (immunotherapy). Hitherto unrecognized problems in the selection of cases, the recording and scoring of symptoms, the tally of medication other than preparation(s) under test and the maintenance of experimental control became apparent (Ref. 1).

b. *Selection of patients.* The selection of patients should be limited of those

giving a clear history of having had allergic symptoms (hay fever) in at least two consecutive annual pollen seasons, who are free from symptoms at other times of the year, who react intensely to prick or scratch test with an extract of the appropriate pollen and who are otherwise in good general health. Patients who are not undergoing treatment with injections of allergenic extracts are preferred in the study.

The diagnosis of allergic rhinitis depends on both a history of the symptoms occurring at the times of allergenic exposure and their absence at other times, and the presence of intense relevant immunologic reactivity commonly determined by skin test. The patient's statements as to the time of year when symptoms occur may be in error. Therefore, documentation of the occurrence of symptoms at the time of exposure and the absence of symptoms at other times by observation of the patient is preferable to the history. Patients who react intensively by skin test to one pollen usually react to several other pollens also. Some of the reactions obtained by skin test may be irrelevant, a positive skin test being a necessary but not sufficient basis for identifying the cause of the symptoms. Thus the limitations of the history and the skin test need to be taken into account.

c. *Methods of study.* Assessment of therapy is based on a subjective response. Therefore, some means of quantitating symptoms must be adopted. Experience has indicated that this can be done satisfactorily by maintaining a daily tally of symptoms specifying type, e.g., sneezing, rhinorrhea, etc., duration in hours per day and intensity. Most patients have little difficulty in describing intensity numerically if they are given an intensity scale wherein points on the scale are defined by statements indicating the degree of discomfort (Refs. 2 and 3). Assignment of a numerical value to the degree of discomfort is space saving and greatly facilitates analysis of the data. However, account should be taken of the burden that a diary imposes on the patient. If too detailed and complicated, patients lose interest and record their symptoms in a perfunctory manner with the result that the data may be worthless. Some compromise between what is ideal and what is practicable must be reached. A satisfactory compromise was one in which the patient was given a symptom score card covering 1 week of study, to be filled out at the end of each day. The patient returned with the card at the end of each week at which time the patient was interviewed and the card rechecked for comprehensibility (Ref. 2). A new card was then supplied.

In a double-blind study which includes a placebo, some patients will suffer severe symptoms and the patient's continuation in the study will thereby be jeopardized. If the design of the study does not permit withdrawal from the study because of severe symptoms as an endpoint, then the investigator will be under great pressure to prescribe or permit use of medication other than the preparations under test or the patient will take medication without reporting having done so. Such medications, if taken, should be recorded accurately on the weekly diary form. Before the study is started, each such drug should be assigned a numerical value per dose based on anticipated efficacy in relieving symptoms of allergic rhinitis. The data may then be incorporated into the analysis at the end of the study.

A placebo identical in appearance and closely similar or identical in taste to the preparation(s) under test must be included in any assessment of drugs for the treatment of allergic rhinitis. Assignment of subjects to the drug(s) under test and the placebo must be random and the code identifying the preparations administered must not be broken until the study is complete.

Patients should be seen throughout the season not less often than every week. Patient diaries should be maintained in which the type, frequency and severity of symptoms and side effects are recorded daily as well as the medication taken. A crossover double-blind design with 30 or more patients is recommended in which each patient takes the test drug or the placebo on alternate weeks. If two dose levels of the test drug are tested, twice the number of patients will be needed.

d. *Interpretation of data.* Results should be subjected to statistical analysis, a p value of 0.05 or less (95 percent confidence or more) being acceptable as evidence of a drug effect. Evidence of drug effectiveness is required from a minimum of three positive studies based on results from three different investigators or laboratories.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

(5) *Evaluation of safety.* The effect of the drug on the hepatic, renal and other systems should be monitored with particular emphasis on systems expected to be influenced by the drug. In the case of the antihistamines the central nervous system is often affected as indicated by such side effects as drowsiness and fatigue. These should not be induced by the drug at a frequency and intensity which might pose a hazard to the patient in the performance of a daily routine.

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2. *Principles in the design of an experimental protocol for testing antihistamine drugs in the "common cold."* a. *Assessment of the use of antihistaminic drugs for the "common cold."* The antihistaminic drugs have been widely used for the treatment of the symptoms of the "common cold." These drugs are usually marketed in combination products with nasal decongestant drugs. It is the Panel's view that this use of the antihistaminic drugs has been based predominantly on clinical impressions and uncontrolled clinical trials, the first of which was published by Brewster in 1947 (Ref. 1). On the other hand, a number of trials have been conducted with double-blind experimental controls but have failed for the most part to substantiate claims for effectiveness. These negative results indicate that if the antihistaminic drugs indeed have a favorable effect on the symptoms of the "common cold," this effect must be of a relatively low order. The subject has been recently reviewed (Ref. 2). The Panel concurs with the authors who stated:

> Many of the reports favoring antihistamine use were published some years ago when a well-controlled, randomized, double-blind clinical trial was not generally recognized as important in the evaluation of therapy. However, results supporting antihistamine use should be interpreted with caution when the research goals are imprecise and the study design permits biases. On the other hand, the findings of the less favorable reports that antihistamines appear not to prevent, abort, or relieve the symptoms of a cold, are supported by only a slightly greater specificity of definition and increased rigor of research methodology. Of all the reports, only two combined precision in definitions and controlled design; their conclusions did not support the use of antihistamines to prevent or relieve the symptoms of a cold. The general lack of specificity in defining disease and research goals and lack of rigor in research design in the majority of all studies is noteworthy. In short, there appears to be little valid evidence that antihistamines have any effect on the common cold.

Studies on the efficacy of the antihistaminic drugs in the treatment of the "common cold" may be misleading if the means of selection do not minimize inadvertent inclusion of subjects with allergic rhinitis, the symptoms of which are similar to those of the "common cold." Relief of symptoms will then be erroneously ascribed to favorable effect of the antihistaminic drugs on the symptoms of the "common cold" when indeed the observed benefit may be attributable to the known efficacy of the antihistaminic drugs in allergic rhinitis. The Panel has earlier discussed in this document both the "common cold" and allergic rhinitis. (See part II. paragraph B.3. above—The "common cold" and part II. paragraph B.6.a. above—Allergic rhinitis.)

The Panel concludes that the effectiveness of the antihistaminic drugs in relieving or allaying the symptoms of the "common cold" has not been established. If further studies on the effectiveness of the antihistaminic drugs in the treatment of the "common cold" are to be carried out, the Panel suggests that particular attention be directed to the selection of subjects and the means of recording symptoms using groups of patients large enough to give statistically meaningful results.

b. *General principles.* The symptoms of allergic rhinitis and the "common cold" have many similarities. A watery

nasal discharge is characteristic of allergic rhinitis and is usual in the "common cold" in the first 1 to 3 days. Sneezing is likewise common to both. Itching of the nose and eyes is more common in allergic rhinitis but also occurs in the "common cold." Nasal congestion occurs in both conditions. Coughing is not a frequent symptom of allergic rhinitis but it occurs in a small percent of cases. Cough likewise occurs in the "common cold," usually in the latter phase of the illness. Fever of low degree may occur in the "common cold," but it is not frequently present. Fever is absent in allergic rhinitis. Watering and redness of the eyes may occur in both conditions (Refs. 3, 4, and 5).

It is commonly stated in texts on allergic disease that examination of the patient with allergic rhinitis reveals swelling within the nose (swollen turbinates) which has a bluish or gray color (Ref. 5), whereas in the "common cold" their color is red (Ref. 4). No studies have been done to test the frequency with which this distinction is diagnostic and its reliability as a means of selecting patients for inclusion in a study of antihistaminic drugs in the treatment of the "common cold" remains uncertain. No other finding on examination appears to be useful in distinguishing between the early phases of the "common cold" and allergic rhinitis.

Because the symptoms of allergic rhinitis and the "common cold" are so similar, the two conditions are readily confused. The reported efficacy of the antihistaminic drugs in the treatment of the "common cold" has been attributed to the inadvertant inclusion of some cases of allergic rhinitis in some studies (Ref. 2) in which condition the antihistaminic drugs are recognized as effective. Unless steps are taken to eliminate subjects with allergic rhinitis from the study population, the results of the study of the "common cold" may be misleading.

c. *Selection of patients.* Since the distinction between allergic rhinitis and the "common cold," especially in its early phases, is difficult or impossible to make on the basis of symptoms and examination, the following means of minimizing inclusion of subjects with symptoms of allergic rhinitis should be adopted:

(1) Subjects giving a history of allergic rhinitis, e.g., hay fever or allergy to animals, should be excluded.

(2) Studies should be done in the months when allergic exposure is less likely and the "common cold" is more prevalent.

Selection of subjects according to these principles will minimize but cannot entirely eliminate the inclusion of some subjects who are having symptoms of allergic rhinitis and not a "common cold."

Subjects selected for the studies should be in good health except for the presence of a "common cold." The symptoms to be evaluated, i.e., runny nose, sneezing, etc., should have been present for 1 day but not longer than 3 days. Fever should be absent or should not exceed 100° F by mouth (adults) or 101° F by mouth (children under 12 years). Those with evidence of bacterial infection of the pharynx (exudative pharyngitis) or who have severe pharyngitis and severe sore throat should be excluded.

d. *Methods of study.* The drug(s) to be tested and a placebo should be identical in appearance and closely similar in taste identifiable by code only. Strict double-blind control throughout the study is essential. The groups of subjects should be matched by age, sex and severity and duration of illness.

Each group should contain 50 to 100 subjects. This large number is considered mandatory for the following reasons: a crossover design is not possible in so short an illness; the assessment is based on a subjective response; there are uncertainties in diagnosis; there is possible heterogeneity of the study population with respect to the type of virus causing the illness; and the effect of the antihistaminic drug in relieving symptoms of the "common cold" is not marked.

Medication other than the preparations in the test should not be taken during the course of the study. The design of the study should be such as to permit determination of each preparation's effect on each type of symptom and the stage in the disease in which this effect takes place. Therefore, each subject should maintain an appropriate tally of the type, duration and intensity of symptoms. The study should be of sufficient length to encompass the entire illness to provide data on all possible effects of the drug under test on the course of the disease. If a subject drops out of the study, the reason for doing so should be determined and recorded.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

e. *Interpretation of data.* A recommended dose of the antihistamine should induce a statistically significant reduction in symptoms when compared to the placebo response. Results should be subjected to statistical analysis, a p value of 0.05 or less (95 percent confidence or more) being acceptable as evidence of a drug effect. A decision on drug effectiveness should be based on demonstrable drug effectiveness in a minimum of three positive comparable double-blind studies based on results from three different investigators or laboratories.

f. *Evaluation of safety.* If the safety of the drug has not been established, then the effect of the drug on the hepatic, renal and other systems should be monitored with particular emphasis on systems expected to be influenced by the drug. In the case of the antihistamines, the central nervous system is often affected, as indicated by such side effects as drowsiness and fatigue. These should not be induced by the drug at a frequency and intensity that might pose a hazard to the patient in the performance of a daily routine.

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VIII. NASAL DECONGESTANTS

A. GENERAL DISCUSSION

A nasal decongestant is an agent which reduces nasal congestion in patients with acute or chronic rhinitis. These agents may be administered topically as drops, sprays or inhaled vapors or orally in a solid or liquid dosage form. The drug effect is brought about by constriction of dilated blood vessels (vasoconstriction) within the nasal mucosa, thus temporarily reducing the swelling associated with inflammation of the mucous membrane lining the nasal passage (Ref. 1).

Topically administered nasal decongestants produce an intense degree of vasoconstriction, a factor responsible for the rapid and pronounced reduction in nasal obstruction. This intense local vasoconstriction also accounts for negligible absorption of the nasal decongestant into the general circulation. Consequently, negligible systemic effects occur following topical use of nasal decongestants unless excessive nasal solution is applied causing drainage into the stomach where it may be absorbed. Studies demonstrating minimal systemic absorption of radioactively labeled oxymetazoline following intranasal application (Ref. 2) and negligible cardiovascular effects following normal and excessive intranasal doses of phenylephrine or xylometrazoline (Refs. 3 through 7) support this point. Because of the remarkable degree of nasal decongestion which follows topical application of these agents, there is the tendency on the part of patients to administer nasal decongestants too frequently and for too long a period of time. Continued and intense drug-induced vasoconstriction can lead to rebound dilation of the blood vessels as the drug effect subsides. This phenomenon, which intensifies nasal congestion and perpetuates the rhinitis condition, has been termed "rebound congestion." This problem is minimized if topically applied decongestants are administered in accordance with label directions at recommended intervals for periods not exceeding 3 days.

Another practical caution with the use of topically applied decongestants is in regard to the possible spread of infection if the drug dispenser is used by more than one person. This can occur if the tip of the dropper or spray container comes in contact with the nose during drug administration.

Some of the nasal decongestants (sympathomimetic amines) are also effective when administered orally. Although the intensity of vasoconstriction in the nasal mucosa and associated symptomatic re-

lief of nasal congestion are less than that produced by the topical application of decongestants, the problem of rebound congestion is not a factor with use of the orally administered nasal decongestants. These orally administered sympathomimetic amines are distributed by the circulation to other target tissues as well as the nasal mucosa and thus produce side effects not seen following use of nasal decongestants topically.

In general, side effects associated with recommended oral doses of OTC nasal decongestants are minimal, but at higher doses may include nervousness, dizziness, and sleeplessness. Individuals with disease conditions which can be aggravated by sympathomimetic drug action, e.g., high blood pressure, heart disease, diabetes mellitus and hyperthyroidism, should not use decongestants orally except under the advice and supervision of a physician. Likewise, patients taking other drugs whose action can intensify the sympathomimetic drug action, e.g., monoamine oxidase inhibitors, should not take nasal decongestants orally except under the advice and supervision of a physician. The Panel does not feel these restrictions should apply to topically applied nasal decongestants when administered in recommended doses because of their localized action, i.e., minimal systemic absorption.

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B. CATEGORIZATION OF DATA

1. *Category I conditions under which nasal decongestant ingredients are generally recognized as safe and effective and are not misbranded.*

Category I Active Ingredients

The Panel has classified the following nasal decongestant active ingredients as generally recognized as safe and effective and not misbranded:

Ephedrine preparations (topical): Ephedrine, Ephedrine hydrochloride, Ephedrine sulfate, Racephedrine hydrochloride
Naphazoline hydrochloride (topical)
Oxymetazoline hydrochloride (topical)
Phenylephrine hydrochloride (oral/topical)
Phenylpropanolamine preparations (oral): Phenylpropanolamine bitartrate, Phenylpropanolamine hydrochloride, Phenylpropanolamine maleate
Propylhexedrine (inhalant)
Pseudoephedrine preparations (oral): Pseudoephedrine hydrochloride, Pseudoephedrine sulfate
Xylometazoline hydrochloride (topical)

a. *Ephedrine preparations (ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine hydrochloride) (topical).* The Panel concludes that ephedrine and its salts are safe and effective as topical nasal decongestants for OTC use as specified in the dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that ephedrine and its salts (topical) are safe in the dosage ranges used as nasal decongestants. Having been introduced from China in 1924 (Ref. 1) there has been a long experience with this drug which is used orally, chiefly from bronchodilation and usually in a dosage of 25 mg 4 times daily and topically in the nose as a 0.5 percent to 3 percent solution (Ref. 2). No reports describing adverse effects when used topically were encountered nor were there studies directed at the question of adverse local effects. Based on general clinical experience with topical nasal decongestants, rebound congestion would be expected with continued use. However, concentrations of 1 percent or less, as judged by the clinical experience of the Panel, would not be expected to cause this reaction if use is limited to a few days.

(2) *Effectiveness.* Extensive clinical experience indicates that ephedrine and its salts in 0.5 to 1 percent concentrations applied as drops or spray have a nasal decongestant effect (Ref. 3). Ephedrine as a prototype of the topical sympathomimetic nasal decongestant agents has been compared to other effective topical nasal decongestants in both objective measurement studies (Ref. 4) and subjective observation of nasal decongestant activity (Refs. 5 and 6) in patients with acute rhinitis. Ephedrine sulfate in 1 percent solution has been demonstrated to induce a prompt nasal decongestant effect which persists at maximal levels for up to 1 hour and gradually declines to pretreatment levels by the 4th hour.

(3) *Dosage.* Adult topical dosage is 2 to 3 drops or sprays in each nostril of a 0.5 percent aqueous solution not more frequently than every 4 hours. Children 6 to under 12 years topical dosage is 1 to 2 drops or sprays of a 0.5 percent solution not more frequently than every 4 hours. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients (see part VIII. paragraph B.1. below—Category I Labeling). In addition, the Panel recommends the following specific labeling: *Warning:* "Do not give this product to children under 6 years except under the advice and supervision of a physician".

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b. *Naphazoline hydrochloride (topical).* The Panel concludes that naphazoline hydrochloride is safe and effective as a topical nasal decongestant for OTC use as specified in the dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that naphazoline hydrochloride (topical) is safe in the dosage ranges used as a nasal decongestant. Studies involving visualization of the nasal mucosa following a single application of naphazoline, 0.05 to 0.1 percent, revealed rebound congestion as a fairly consistent sequel to the 4 to 6 hour period of nasal decongestion (Refs. 1 and 2). The tendency for frequent and continued use due to rebound congestion has been reported by several authors (Refs. 3 through 6). The continued use of naphazoline hydrochloride may result in dependence. To avoid this dependence, naphazoline use should not exceed 3 days duration.

In infants and young children, nasal administration as well as accidental ingestion of 0.05 to 0.1 percent naphazoline have been associated with systemic effects such as sedation, nervousness, increase in systolic blood pressure and bradycardia (Refs. 7 through 13). Furthermore, because rebound congestion with naphazoline is also a problem in infants, this nasal decongestant should probably not be used in children under 6 years (Ref. 1). For children 6 to 12 years, the pediatric concentration of 0.025 percent, should be used to minimize exposure to excess quantities of the drug.

(2) *Effectiveness.* Single dose applications of naphazoline, 0.1 percent in adult rhinitis patients using objective meas-

urement, revealed onset of nasal decongestion within 10 minutes and persisting up to 6 hours (Refs. 2 and 14). A single-dose objective measurement study in children demonstrated nasal decongestion of up to 5 hours duration (Ref. 1). The number and ages of the children and the concentration of naphazoline were not specified. In one study involving repeated administration of 0.05 percent naphazoline drops over a 1-week period, 34 of 35 patients experienced satisfactory nasal decongestion as judged subjectively by the patient and by visualization of the nasal mucosa (Ref. 15).

(3) *Dosage.* Adult topical dosage is 1 to 2 drops or sprays of a 0.05 percent aqueous solution in each nostril not more frequently than every 6 hours. Children 6 to under 12 years topical dosage is 1 to 2 drops or sprays of a 0.025 percent aqueous solution in each nostril not more frequently than every 6 hours. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warnings.* (i) *For products containing a concentration of 0.025 percent naphazoline hydrochloride:* "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(ii) *For products containing a concentration of 0.05 percent naphazoline hydrochloride:* "For adult use only. Do not give this product to children under 6 years since it may cause sedation if swallowed".

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c. *Oxymetazoline hydrochloride (topical).* The Panel concludes that oxymetazoline hydrochloride is safe and effective as a topical nasal decongestant for OTC use as specified in the dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that oxymetazoline hydrochloride (topical) is safe in the dosage ranges used as a nasal decongestant. Because the decongestant effect of oxymetazoline hydrochloride administered as drops or spray persists up to 5 to 6 hours and gradually declines thereafter, rebound congestion after single administration is negligible (Ref. 1). Twice a day dosing which should give adequate relief of nasal congestion should be expected to have a negligible incidence of rebound congestion. Several studies in adults with chronic rhinitis using either 0.05 percent drops or spray for 2 days to 4 weeks support this contention (Refs. 2 through 5). In one study 92 chronic rhinitis patients used 0.05 percent oxymetazoline spray in one nostril and 0.25 percent phenylephrine spray in the other nostril for 2 weeks. In this double-blind study rebound congestion was subjectively noted in one-third of the oxymetazoline-treated nostrils and two-thirds of the phenylephrine-treated nostrils (Ref. 6). No rebound congestion was noted over a 6 hour observation period following 5 drops of 0.025 percent oxymetazoline in each nostril of 33 children with allergic rhinitis (Ref. 7). In 30 children ages 4 to 10 years with allergic rhinitis, treatment with 0.025 percent oxymetazoline, 3 drops in each nostril 3 times a day, was associated with no loss of effectiveness during a 2-week treatment period as measured by electronic posterior rhinometry and no rebound congestion in a 2 week posttreatment evaluation period (Ref. 8).

Animal studies with radioactively labeled oxymetazoline indicate that the rate of systemic absorption from nasal application is too slow to achieve pharmacologic levels in the plasma (Ref. 9). Furthermore, double-blind studies in healthy adults reveal that 1.8 mg, the equivalent of 3.6 ml of a 0.05 percent solution, was the minimal orally administered dose of oxymetazoline producing any measurable effect on the cardiovascular system. Nonspecific EKG changes were not accompanied by blood pressure or heart rate changes (Ref. 10).

Because of these safety considerations the Panel recommends that oxymetazoline, which is currently a drug available only by prescription, be reclassified to permit OTC use as well.

(2) *Effectiveness.* In a double-blind subjective evaluation study, 92 adult patients with chronic rhinitis judged oxymetazoline, 0.05 percent spray, to induce nasal decongestion of 4 to 8 hours duration (Ref. 6). Objective studies in 20 patients with either chronic rhinitis due to allergy or acute rhinitis due to head cold showed effectiveness of a 0.05 percent oxymetazoline spray in two-thirds of the patients with airways still twice pretreatment size at the end of 6 hours (Ref. 1).

In a double-blind subjective evaluation study in 14 children, 2 to 6 years of age with allergic rhinitis, complete opening of the nasal airway was restored for 9 to 12 hours in 7 of the 14 patients receiving 1 drop of 0.025 percent oxymetazoline solution per nostril 2 times daily (Ref. 11). Objective studies in 30 children with allergic rhinitis, ages 4 to 10 years, receiving 0.025 percent oxymetazoline, 3 drops per nostril 3 times daily revealed persistent effectiveness over a 2-week treatment period (Ref. 8).

(3) *Dosage.* Adults and children 6 to under 12 years topical dosage is 2 to 3 drops or sprays of a 0.05 percent aqueous solution in each nostril 2 times daily (in the morning and evening). Children 2 to under 6 years topical dosage is 2 to 3 drops of a 0.025 percent aqueous solution in each nostril 2 times daily (in the morning and evening). Only drops should be used in children 2 to under 6 years since the spray is difficult to use in the small nostril. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling).

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d. *Phenylephrine hydrochloride (oral/topical).* The Panel concludes that phenylephrine hydrochloride is safe and effective as an oral and as a topical nasal decongestant for OTC use as specified in the dosage section discussed below.

(1) *Safety.* (i) *As an oral nasal decongestant:* Clinical experience has confirmed that phenylephrine hydrochoride is safe in the dosage ranges used as an oral nasal decongestant.

Key and Violante reported that oral doses of 40 to 60 mg phenylephrine are necessary for consistent clinically meaningful cardiovascular effects such as increased diastolic pressure and reflex cardiac slowing (Ref. 1). Various reports reinforce the impression that in normal volunteers, blood pressure and pulse rate responses to 10 to 15 mg oral doses are equal to or only minimally greater than placebo. The maximum blood pressure increase does not exceed 2 to 7 mm Hg and the pulse rate changes do not exceed ±6 beats/minute. At doses of 25 mg, blood pressure increases up to 7 mm Hg and pulse changes of ±4–13 beats per minute were occasionally noted at some time intervals (Refs. 1 through 11). If patients were also receiving MAO inhibitors, however, even 10 mg doses of phenylephrine can induce clinically significant cardiovascular responses (Ref. 12).

Overtly perceived side effects at 10-mg doses approximate the incidence and pattern of a placebo response, whereas 15 to 25-mg doses are associated with an increasing incidence of symptoms related to mild central nervous system stimulation (Ref. 1).

(ii) *As a topical nasal decongestant:* Clinical experience has confirmed that phenylephrine hydrochloride is safe in the dosage ranges used as a topical nasal decongestant. Gundrum, Stambuck and Gaines reported a study in which supratherapeutic doses of 0.25 percent phenylephrine drops were chronically administered to rabbits (Ref. 13). The animals were given drops in each nostril either 3 times daily for 10 days or 10 times daily for 3 days. Examination of nasal tissue sections removed from these treated animals revealed no gross or microscopic changes from normal nasal mucosa.

Objective measurement studies showed transient rebound congestion in 3 of 12 adult rhinitis patients during 3 days of treatment with 0.5 percent phenylephrine spray (Ref. 14). Two thirds of 92 chronic rhinitis patients using 0.25 percent phenylephrine spray for 2 weeks noted rebound congestion (Ref. 15). Rhinoscopic observation revealed rebound congestion in 4 of 33 children following single doses of 0.25 percent phenylephrine drops, 5 drops in each nostril (Ref. 16).

Groups of patients with either cardiac, hypertensive and hyperthyroid disorders or diabetes mellitus were administered 5 drops of 0.25 percent or 1 percent phenylephrine solution into each nostril remaining in a head-low position for several minutes to maximize contact time (Refs. 17 and 18). No marked changes in blood pressure control readings were noted over a 45-minute observation period.

(2) *Effectiveness.* (i) *As an oral nasal decongestant:* Clinical studies have documented the effectiveness of phenylephrine as an oral nasal decongestant.

A series of five double-blind crossover placebo-controlled studies over a 3-year period in one laboratory revealed oral doses of phenylephrine from 5 to 25 mg to induce objectively measurable nasal decongestion when compared to placebo in patients with head cold as determined by an anterior rhinometry procedure (Refs. 5 through 9, and 19). Onset time was in 15 to 20 minutes with a duration of 2 to 4 hours. Maximum nasal decongestant effect was associated with the 25 mg dose. Two other laboratories conducted five similarly designed experiments, but because of greater apparent placebo response and variability in inpatient response the studies could not demonstrate a statistically significant difference of 10 to 25 mg from placebo (Refs. 20 through 24).

Subsequent studies measuring nasal airway resistance in head cold patients demonstrated significant nasal decongestant responses to 10 to 25 mg phenylephrine (Ref. 10). In these studies, 25 mg induced a maximal reduction of nasal resistance approaching that reported for noncongested normals, and 10 to 15 mg doses were clinically equivalent in inducing a decrease of nasal resistance about ⅔ maximal. Onset of these effects occurred within 15 minutes. The maximum effect occurred within 30 to 90 minutes with a gradual decline thereafter. A double-blind crossover study in 20 chronic rhinitis patients, however, could demonstrate no significant decrease in nasal airway resistance as compared to placebo with 10, 20, or 40 mg of phenylephrine, orally, over a 4-hour observation period (Ref. 25). In this study, phenylpropanolamine 40 mg and pseudoephedrine 60 mg each produced a significant decrease in nasal airway resistance persisting for at least 3 hours.

A recent double-blind controlled study involving 50 adult patients with nasal congestion associated with the "common cold" (25 patients in each group) demonstrated that a single oral 10 mg dose of phenylephrine led to a reduction in nasal airway resistance averaging 11 percent at 15 minutes, 21 percent at 30 minutes, 28 percent at 60 minutes and 26 percent at 120 minutes (Ref. 26). These reductions were all significantly different from placebo at the corresponding measurement times. These 50 patients were part of a 200-patient subjective evaluation study group with nasal congestion associated with the "common cold", 100 of each who received either 10 mg phenylephrine or placebo at 4-hour intervals over a 12-hour period. Patient subjective evaluation revealed that the phenylephrine treatment group experienced relief of nasal congestion, runny nose and sneezing throughout the 12-hour observation period. Symptom relief in each case was significantly different from that reported by the placebo group (Ref. 26).

(ii) *As a topical nasal decongestant:* In a double-blind crossover placebo-controlled study, phenylephrine was given as a 0.5 percent spray, 1 spray in each nostril repeated in 3 minutes, to one group of 16 patients with head cold and one group of 9 patients with allergic rhinitis. Objective measurements using both posterior electronic rhinometry and body plethysmography revealed significant nasal decongestion at the 30- and 60-minute recording times (Ref. 27).

In another study using 0.5 percent phenylephrine spray in 12 adult rhinitis patients, objectively measured nasal decongestant effects persisted from 1 to 3 hours following administration (Ref. 14). In a 2-week subjective evaluation study of phenylephrine 0.25 percent spray in 92 chronic rhinitis patients, the duration of effect following each dose was generally reported to be 4 hours or less (Ref. 15).

(3) *Dosage.* (i) *As an oral nasal decongestant:* Adult oral dosage is 10 mg every 4 hours not to exceed 60 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 mg every 4 hours not to exceed 30 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 mg every 4 hours not to exceed 15 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(ii) *As a topical nasal decongestant:* Adult topical dosage is 2 to 3 drops or sprays in each nostril of a 0.25 to 0.5 percent aqueous solution not more frequently than every 4 hours. Children 6 to under 12 years topical dosage is 2 to 3 drops or sprays in each nostril of a 0.25 percent aqueous solution not more frequently than every 4 hours. Children 2 to under 6 years topical dosage is 2 to 3 drops in each nostril of a 0.125 percent aqueous solution not more frequently than every 4 hours. Only drops should be used in children 2 to under 6 years since the spray is difficult to use in the small nostril. For children under 2 years, there

is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* (i) *As an oral nasal decongestant:* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling.)

(ii) *As a topical nasal decongestant:* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warnings: (a) For products containing a concentration of 0.125 percent phenylephrine hydrochloride:* "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(b) For products containing a concentration of 0.25 percent phenylephrine hydrochloride: "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(c) For products containing a concentration of 0.5 percent phenylephrine hydrochloride: "For adult use only. Do not give this product to children under 12 years except under the advice and supervision of a physician".

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e. *Phenylpropanolamine preparations (phenylpropanolamine bitartrate, phenylpropanolamine hydrochloride, phenylpropanolamine maleate) (oral).* The Panel concludes that phenylpropanolamine and its salts are safe and effective as oral nasal decongestants for OTC use as specified in the dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that phenylpropanolamine and its salts (oral) are safe in the dosage ranges used as nasal decongestants. Phenylpropanolamine is one of the most frequently used oral nasal decongestants, similar in action to ephedrine but with less central nervous system stimulation (Ref. 1). Subjective evaluation studies reveal that, in adults, phenylpropanolamine in plain capsules in doses up to 50 mg every 3 hours is associated with overt side effects either equal to or only slightly exceeding those of placebo. The side effects consisted of nervousness, insomnia, motor restlessness and nausea (Refs. 2 and 3).

Boyer reported three patients with prostatic hypertrophy who complained of urinary retention following ephedrine dosing but had no urinary retention at effective nasal decongestant doses of phenylpropanolamine (Ref. 3).

In three reports involving a total of over 200 children ages 2 to 15, phenylpropanolamine, in age-related doses of 6.25 to 25 mg 4 times daily in combination with acetaminophen and in one study also with phenyltoloxamine, was subjectively observed to relieve symptoms of nasal congestion with a low incidence of side effects (Refs. 4 through 6).

Individuals with normal blood pressure receiving phenylpropanolamine alone, either as a 50 mg plain capsule 4 times daily or as a 50 mg sustained release capsule 2 times daily had no significant effect on blood pressure or pulse rate. No adverse effect on cardiovascular systems was noted after 5 to 42 days of treatment (Refs. 7 through 10). Intravenous administration of phenylpropanolamine induced dose-related systolic blood pressure increases in humans. A 16 to 28 mm increase following 20 to 25 mg and a 44 to 82 mm increase following 50 mg were observed (Ref. 11).

Phenylpropanolamine 50 mg, in sustained release combination with belladonna alkaloids 0.2 mg, and chlorpheniramine 4 mg, was administered 2 times daily for 7 days to groups of patients with normal anterior chamber angle, with narrow angle but no glaucoma signs and to patients with frank glaucoma controlled by medication. No drug-induced alteration of intraocular tension was evidenced in any of the 3 groups of subjects (Refs. 12 and 13).

There have been isolated "letter to the editor" reports of individuals consuming therapeutic doses of phenylpropanolamine-containing preparations and experiencing an acute hypertensive episode (Ref. 14). Details relative to other contributing factors are usually too vague to determine if the phenylpropanolamine was entirely responsible. One "letter" reported an acute overdose of a sustained release phenylpropanolamine combination product, eight spansules containing 50 mg of phenylpropanolamine in combination with isopropamide and diphenylpyraline, was followed within 2 hours by an acute hypertensive response, severe headaches, restlessness and vomiting (Ref. 15).

One paper cited three cases of "psychotic episodes" associated with presumably therapeutic doses of phenylpropanolamine 50 mg, in combination with isopropamide and phenyltoloxamine (Ref. 16). The authors indicated that personality changes following phenylpropanolamine preparations were not an uncommon occurrence in patients in their hospitals.

In summary then, at therapeutic doses of phenylpropanolamine taken orally, the incidence of side effects in adults and

children is low. There have been isolated reports, however, of individuals experiencing idiosyncratic reactions of central nervous system stimulation and/or blood pressure rise following therapeutic doses. These effects would also be expected in most individuals with acute overdoses of the drug.

Prior MAO inhibitor treatment has been clearly shown to potentiate dangerously the blood pressure elevating effects of 30 to 50 mg phenylpropanolamine (Refs. 17 through 20).

A single incident was reported of phenylpropanolamine 50 mg, in combination with chlorpheniramine and isopropamide, antagonizing the antihypertensive effect of bethanidine sulfate, an analogue of guanethidine sulfate (Ref. 21). The antihypertensive effect of guanethidine can be antagonized by concurrent administration of amphetamine (Ref. 22). Current evidence suggests that phenylpropanolamine, being structurally similar to amphetamine, might be expected to exert a similar antagonistic effect (Ref. 23). However, this effect is important to note but not sufficiently documented to elicit a warning statement.

(2) *Effectiveness.* Three of five objective, double-blind, crossover studies comparing phenylpropanolamine with placebo in patients with chronic nasal congestion have demonstrated oral nasal decongestant effectiveness in 25 to 40 mg doses.

The earliest report, using anterior rhinometry in 88 patients, some with acute and some with chronic nasal congestion, showed that ephedrine sulfate 25 mg, orally was significantly better than placebo at the 1-hour time period; but phenylpropanolamine hydrochloride 25 mg, as well as pseudoephedrine hydrochloride, 60 mg, and phenylephrine hydrochloride 10 mg, were not significantly different from placebo. In this crossover study the patients were tested on 5 consecutive days (Ref. 24).

The second study measuring in 12 patients nasal airway resistance at a flow rate of 0.5 l/second demonstrated phenylpropanolamine hydrochloride 18 mg orally to yield greater reduction in nasal airway resistance from pre-drug state than placebo throughout a 4-hour period of observation. The validity of these results is unclear since acetaminophen 325 mg orally also induced a similar magnitude of response in this test (Ref. 25).

A similar followup study in 12 patients by the same author did show significant difference between phenylpropanolamine 25 mg orally and placebo during a 4-hour observation period (Ref. 26).

This author then compared 3 successive doses of 25 mg at 4-hour intervals with a single 75-mg dose in a timed-release formulation in a crossover design in 12 patients and demonstrated continued reduction in nasal airway resistance throughout a 13-hour test period in both cases (Ref. 27). Urinary excretion of phenylpropanolamine, administered as a 75-mg timed-release capsule, approximates 3 doses of 25 mg administered at 4-hour intervals (Ref. 28). Although blood level data more directly reflect rate of drug absorption and drug level at sites of action, these urinary excretion data are consistent with the sustained decrease in nasal airway resistance obtained with a 75 mg timed-release capsule and three consecutive doses of 25 mg.

Another investigation measuring nasal airway resistance at a flow rate of 0.2 l/second in trained volunteers, demonstrated that phenylpropanolamine 40 mg orally induces a peak affect up to 3 hours with gradual return toward control thereafter (Refs. 29 and 30). This investigator also demonstrated that a timed-release formulation of phenylpropanolamine hydrochloride 50 mg in combination with belladonna alkaloids 0.2 mg and chlorpheniramine maleate 4 mg induced a significant decrease in nasal resistance compared to placebo over a 10-hour testing interval (Ref. 31).

(3) *Dosage.* Dosages are based on the phenylpropanolamine hydrochloride equivalent. Adult oral dosage is 25 mg every 4 hours or 50 mg every 8 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 mg every 4 hours or 25 mg every 8 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is 6.25 mg every 4 hours or 12.5 mg every 8 hours not to exceed 37.5 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B. 1. below—Category I Labeling.)

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f. *Propylhexedrine (inhalant).* The Panel concludes that propylhexedrine (inhalant) is safe and effective as an inhalant nasal decongestant for OTC use as specified in the dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that propylhexedrine (inhalant) is safe in the dosage ranges used as a nasal decongestant. Because of a wide margin of safety and the relative freedom from toxic effects, use by inhalation is not contraindicated for patients in whom an ephedrine-like pressor or stimulant action would be undesirable (Ref. 1). Excessive doses, at least six inhalations per nostril, of propylhexedrine inhaler produced no undesirable side effects such as angina attacks, ECG changes, or vasopressor responses in 20 patients with history of severe angina pectoris due to arteriosclerosis (Ref. 2). Two inhalations of propylhexedrine inhaler, 250 mg per inhaler, is reported to deliver approximately 0.5 mg of the volatile amine to the nostril (Ref. 3).

Oral doses of propylhexedrine alone, 100 mg, in normal adults induces a 17 to 23 mm blood pressure rise and reflex bradycardia but no overt symptoms of euphoria, palpitation or dry mouth (Ref. 4). Another investigator reported that 250 mg by mouth induced only slight nervousness, anxiety and tachycardia (Ref. 5). A 3-year old who ingested 15 tablets of propylhexedrine, a total dose of 375 mg, developed pronounced symptoms of central nervous stimulation consisting of insomnia, tremor, muscular hypertonicity and tachycardia which subsided in 3 days (Ref. 6). Propylhexedrine is marketed outside of the United States as an anorexic.

One individual ingesting the contents of a propylhexedrine inhaler containing 250 mg of amine plus menthol and lavender oil, developed an extreme illness lasting 4 weeks and involved "shock lung" syndrome (Ref. 7). Two notes report psychotic behavioral changes in persons with a habit of chewing the inhaler or dissolving the contents in coffee and consuming it (Refs. 8, 9, and 10).

Rats inhaling propylhexedrine, 0.55–0.70 mg/800 ml air, for 6 to 10 minute periods daily for 30 days revealed no histological evidence of tracheobronchial mucosal irritation (Ref. 11). A double-blind study was undertaken to assess the effect of inhaler administration every 4 hours of propylhexedrine plus menthol vapors to 20 normal human volunteers and menthol vapors alone to 18 normal human volunteers over a 2-week period (Ref. 12). Nasal airway resistance measurements on days 1, 7 and 14 revealed no evidence of diminished responsiveness to the propylhexedrine inhaler with this repeated use. The results indicate that under these conditions of dosing, rebound congestion is not a prominent feature.

(2) *Effectiveness.* Four noncontrolled subjective evaluation studies of propylhexedrine inhaler in a total of 140 patients with various types of nasal congestion problems revealed subjective improvement with minimal side effects. Slight stinging occurred in some cases (Refs. 13 and 14). In one of these studies of 20 patients, the onset of subjective relief was noted between 30 seconds to 5 minutes following two inhalations per nostril with "clear nasal breathing" reported to persist for 30 to 120 minutes.

A recent well-controlled double-blind trial of adults with head colds has been done with inhalers containing either propylhexedrine plus menthol or menthol alone, and using single nostril airway resistance measurements (Ref. 15). Unfortunately, propylhexedrine alone was not used. However, menthol in an inhaler alone appeared to have no significant effect on nasal airway resistance but menthol plus propylhexedrine did significantly reduce nasal airway resistance for about 2 hours with a maximum effect at about 30 minutes. It should be noted that two inhalations were used in one nostril and then repeated after 2 hours. Measurements made 4 hours after the initial inhalation, that is, 2 hours after the repeat inhalation, suggest a possible rebound congestion.

A subsequent double-blind objective measurement study by another investigator compared the nasal decongestant effect of a propylhexedrine inhaler with a placebo inhaler in 50 adult patients with nasal congestion due to head cold, divided equally between active and placebo group (Ref. 16). Following a control period for recording baseline nasal airway resistance, each patient administered two inhalations per nostril from their coded inhaler. Nasal airway resistance (NAR) measured at intervals up to 4 hours demonstrated significant decrease in NAR in the propylhexedrine group compared to placebo for up to 90 minutes and decline toward control levels thereafter. These results were associated with patient perception of decreased nasal congestion during the first 90 minutes. In this single dose administration study no side effects or evidence of rebound congestion was noted.

(3) *Dosage.* Adults and children 6 to under 12 years inhalant dosage from an inhaler that shall deliver in each 800 ml of air 0.40 to 0.50 mg of propylhexedrine is 2 inhalations in each nostril not more frequently than every 2 hours. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician. The inhaler should retain effectiveness for a minimum of 2 to 3 months.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling.)

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g. *Pseudoephedrine preparations (pseudoephedrine hydrochloride, pseudoephedrine sulfate) (oral).* The Panel concludes that the pseudoephedrine and its salts are safe and effective as oral nasal decongestants for OTC use as specified in the dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that pseudoephedrine and its salts (oral) are safe in the dosage ranges used as nasal decongestants. In a series of 21 patients who took 60 mg of pseudoephedrine orally, mild side effects such as drowsiness, insomnia, and headache occurred in six of these patients (Ref. 1).

In a study of cardiovascular effects, dose responses in four subjects showed that 210 to 240 mg or 3.0 to 3.4 mg/kg were required to raise diastolic blood pressure to 90 mm Hg or above (Ref. 2).

Acute blood pressure rises may occur, however, if pseudoephedrine in therapeutic doses is taken with MAO inhibitors (Refs. 3 and 4).

(2) *Effectiveness.* A double-blind subjective study in allergic rhinitis patients showed pseudoephedrine to be better than placebo (Ref. 1). In children, a double-blind subjective study showed pseudoephedrine to be better than placebo in allergic respiratory disease and possibly also in non-allergic respiratory conditions, but no statistics are given (Ref. 5). In a study of 88 patients, there were no differences between the drug and placebo group subjectively or by rhinometry (Ref. 6). However, significant increases in na-

sal flow rates up to 20 percent after 60 mg orally and lasting at least 2 hours have been shown in other series (Refs. 7 and 8). Recent work with measurements of nasal airway resistance confirms a nasal decongestant effect, after an oral dose of 60 mg lasting up to 4 hours and returning to control values by 6 hours (Ref. 9).

(3) *Dosage.* Adult oral dosage is 60 mg every 4 hours not to exceed a maximum of 360 mg in 24 hours. Children 6 to under 12 years oral dosage is 30 mg every 4 hours not to exceed 180 mg in 24 hours. Children 2 to under 6 years oral dosage is 15 mg every 4 hours not to exceed 90 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling).

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h. *Xylometazoline hydrochloride (topical).* The Panel concludes that xylometazoline is safe and effective as a topical nasal decongestant for OTC use as specified in the dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that xylometazoline hydrochloride (topical) is safe in the dosage ranges used as a nasal decongestant. Because the decongestant effect of xylometazoline hydrochloride, administered as drops or sprays, persists up to 5 hours with gradual decline thereafter, objective measurement studies in adults revealed no rebound congestion after single administration of 0.05 or 0.1 percent solutions (Refs. 1 through 4). Both objective and subjective measurement studies of 0.05 percent xylometazoline in infants and 0.05 or 0.1 percent, in children, reveal negligible rebound congestion with 3 times daily dosing for periods of 2 days to 2 weeks (Refs. 5 through 9). No cardiovascular changes were produced by nasal application of xylometazoline (Refs. 5, 7, and 10). Because of these safety considerations, the Panel recommends that xylometazoline, which is currently a drug available only by prescription, be reclassified to permit OTC usage as well.

(2) *Effectiveness.* Objective measurement studies in acute and chronic rhinitis among adults showed a single application of xylometazoline, 0.1 percent drops or sprays, to induce a rapid (5 to 10 minutes) and a prolonged (up to 10 hours) decrease, in nasal airway resistance (Refs. 1 through 4). In infants and children, objective measurement studies (Ref. 5) and subjective evaluation (Refs. 7, 9, and 11) demonstrated the nasal decongestant effectiveness of 0.01, 0.05 and 0.1 percent xylometazoline drops or sprays.

(3) *Dosage.* Adult topical dosage is 2 to 3 drops or sprays in each nostril of a 0.1 percent aqueous solution every 8 to 10 hours. Children 2 to under 12 years topical dosage is 2 to 3 drops or sprays in each nostril of a 0.05 percent aqueous solution every 8 to 10 hours. Only drops should be used in children 2 to under 6 years since the spray is difficult to use in the small nostril. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warnings:* (i) *For products containing a concentration of 0.05 percent xylometazoline hydrochloride:* "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(ii) *For products containing a concentration of 0.1 percent xylometazoline hydrochloride:* "For adult use only. Do not give this product to children under 12 years except under the advice and supervision of a physician".

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Category I Labeling

The Panel recommends the following Category I labeling for nasal decongestant active ingredients to be generally recognized as safe and effective and not misbranded as well as the specific labeling discussed in the individual ingredient statements:

a. *Indications.* (1) "For temporary relief of nasal congestion due to the common cold".

(2) "For temporary relief of nasal congestion due to hay fever or other upper respiratory allergies".

(3) "For temporary relief of nasal congestion associated with sinusitus".

(4) "For the temporary relief of stuffy nose (stopped up nose, nasal stuffiness, clogged up nose)".

(5) "Reduce swelling of nasal passages; shrinks swollen membranes".

(6) "Decongests nasal passages".

(7) "Temporarily restores freer breathing through the nose".

(8) "Helps clear nasal passages".

(9) "Helps decongest sinus openings, sinus passages".

(10) "Promotes nasal and/or sinus drainage".

(11) For products with claims for duration of effect: Statements as to duration of effect must be substantiated and

accompanied by a specific time period expressed in minutes or hours, as appropriate.

(12) For products used as topical nasal decongestants with claims for rapid onset of action: Statements relating to time to onset of action, such as, "fast" or "quick", must be accompanied by a specific time period expressed in minutes.

(13) For topical nasal decongestants which can demonstrate a cooling sensation: (i) "Provides cooling sensation".

(ii) "Cooling".

(iii) "Cools nasal passages".

b. *Warnings.* (1) *For products used as topical nasal decongestants:* (i) "Do n t exceed recommended dosage because symptoms may occur such as burning, stinging, sneezing, or increase of nasal discharge".

(ii) "Do not use this product for more than 3 days. If symptoms persist, consult a physician".

(iii) "The use of this dispenser by more than one person may spread infection".

(2) *For products used as oral nasal decongestants:* (i) "Do not exceed recommended dosage because at higher doses nervousness, dizziness, or sleeplessness may occur".

(ii) "If symptoms do not improve within 7 days or are accompanied by high fever, consult a physician before continuing use".

(iii) "Do not take this product if you have high blood pressure, heart disease, diabetes or thyroid disease except under the advice and supervision of a physician.

(iv) *"Drug interaction precaution:* Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor except under the advice and supervision of a physician".

(3) *For products used as inhalant nasal decongestants:* (i) "This inhaler should be warmed in the hand before use to increase effectiveness".

(ii) "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(iii) "Children should not have unsupervised access to this inhaler".

(iv) *"Caution:* Not for use by mouth".

2. *Category II conditions under which nasal decongestant ingredients are not generally recognized as safe and effective or are misbranded.* The use of nasal decongestants under the following conditions is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel concludes that the following active ingredients and labeling should be removed from the market until scientific testing supports its use.

Category II Active Ingredients

The Panel has classified the following nasal decongestant active ingredients as not generally recognized as safe and effective or as misbranded:

Mustard oil (allylisothiocyanate) (topical/inhalant)

Turpentine oil (spirits of turpentine) (oral)

a. *Mustard oil (allylisothiocyanate) (topical/inhalant).* The Panel concludes that mustard oil is neither safe nor effective for topical or inhalant OTC use as a nasal decongestant.

(1) *Safety.* Mustard oil is obtained from Black mustard. Black mustard, which is official in the National Formulary XI, consists of dried, ripe seeds from various varieties of either or both of two species of the genus *Brassica (Cruciferae)*, namely, *Brassica nigra* (Brown mustard) and *Brassica juncea* (Chinese mustard) (Ref. 1). The formation of the irritant constituent, allylisothiocyanate (active ingredient), in black mustard seed results from the hydrolytic activity of the enzyme mirosin, on a glycoside substrate sinigrin (potassium mironate). Allylisothiocyanate is designated as the volatile oil of mustard (Ref. 1), as opposed to the fixed (expressed) oil of mustard, which is composed chiefly of the glycerides of oleic, arachidic, and other fatty acids (Ref. 2). Allylisothiocyanate, the volatile oil of mustard, is isolated from black mustard by distillation (Ref. 3).

The active ingredient of mustard oil, allylisothiocyanate, is present in about 0.6 percent concentration in mustard seed powder. Mustard powder, because of this substance, is a local irritant which has been used in topically applied preparations, e.g., "mustard plaster," for its rubefacient and counterirritant effects and by oral administration for its emetic effect. The vapors of mustard oil are reported to cause irritation of conjunctival, nasal and bronchial mucosa (Refs. 4, 5, and 6). A 15 percent solution of mustard oil in liquid petrolatum has been used to induce mucosal inflammation in an experimental protocol to study anti-inflammatory agents (Refs. 4 and 7).

The Panel is unable to determine a safe dose for mustard oil for topical use or as an inhalant that is also effective as a nasal decongestant.

(2) *Effectiveness.* The effectiveness of mustard oil as a nasal decongestant is uncertain. Black mustard has been used for centuries as a rubefacient and a counterirritant. Mustard plaster, a poultice type of medicament, is used for relieving the pain resulting from bruises and sprains. Mustard preparations are commonly used internally as emetics and as food condiments (Ref. 1). The usual emetic dose of black mustard is 10 gm (Ref. 8).

There is no evidence to support the effectiveness of mustard oil (allylisothiocyanate) as a nasal decongestant when applied topically or used as an inhalant. The Panel is aware that the official preparation Mustard Plaster, National Formulary XI, is indicated for use as a local irritant. The Panel is also aware of a marketed product containing mustard oil in combination with other volatile oils for OTC use. The product is administered by inhalation from the cork that seals the OTC medicine vial (Ref. 9). There is no evidence in the literature that this oil or its active ingredient, allylisothiocyanate, possesses nasal decongestant properties. Literature sources all refer to the local irritant effect only (Refs. 4, 5, 8, and 9).

(3) *Evaluation.* The Panel is unable to determine a safe topical or inhalant dosage for mustard oil for use as a nasal decongestant. The Panel is of the opinion that the risk from topical or inhalant administration outweighs whatever benefit might occur. Therefore, the Panel concludes that mustard oil is not safe for topical or inhalant use as a nasal decongestant.

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b. *Turpentine oil (spirits of turpentine) (oral).* The Panel concludes that oil of turpentine is not safe for OTC use when taken orally as a nasal decongestant.

(1) *Safety.* Oil of turpentine is a volatile oil distilled from turpentine, an oleoresin obtained from the pine tree. It has a characteristic odor and taste. The substance has been administered orally, topically, and by inhalation.

In doses of 15 ml in children and 150 ml in adults, fatal poisoning may occur (Ref. 1). Excessive oral doses produce marked irritation of the alimentary tract, especially of the stomach and of the pelvic organs. Toxic symptoms include vomiting, diarrhea, acute pain, renal irritation, bloody stools and hyperemia of all abdominal organs. Continued use may lead to cloudy swelling and fatty degeneration of the liver. Abnormal central nervous system symptoms may develop (Refs. 2 and 3).

Since no safe oral dose has been established for effective use as a nasal decongestant, the Panel concludes that turpentine oil should not be available for oral OTC use as a nasal decongestant. However, elsewhere in this document, the Panel concludes that the ingredient is safe when applied topically or used as

an inhalant but that there are insufficient data to permit final classification of its effectiveness for inhalant or topical use as a nasal decongestant. (See part VIII. paragraph B.3.m. below—Turpentine oil (spirits of turpentine) (topical/inhalant).)

(2) *Effectiveness.* Oil of turpentine is irritating and its chief suggested uses are based on this property (Refs. 1 and 4). There is no evidence to support its effectiveness as a nasal decongestant when taken orally.

(3) *Evaluation.* The Panel is unable to determine a safe oral dosage for turpentine oil for use as a nasal decongestant. The Panel is of the opinion that the risk from oral administration outweighs whatever benefit might occur. Therefore, the Panel concludes that turpentine oil is not safe for oral use as a nasal decongestant.

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Category II Labeling

All claims that state or imply a therapeutic action or safety property peculiar to the preparation that cannot be demonstrated in controlled studies are not acceptable. The Panel has previously discussed such labeling. (See part II. paragraph O. above—CCABA Product Labeling Claims Not Supported by Scientific Evidence.) However, labeling that is descriptive of the product such as its taste or appearance are acceptable.

The Panel concludes that the examples of language expressed in the following misleading claims are excessive and claims either too much or claims effects which do not occur and therefore such labeling should be removed from the market until scientific testing supports their use:

a. *Topical nasal decongestants.* (1) Reference to "germ-laden mucous" is unacceptable because it implies a curative action rather than symptom-relieving.

(2) The statement "Seldom causes rebound distress like others" is unacceptable because Category I topical nasal decongestants if used in accordance with labeled instructions as to dose and frequency should seldom cause rebound distress.

(3) The term "nonirritating base" is unacceptable because it may encourage a misleading conclusion about the safety characteristics of the total product.

b. *Oral nasal decongestants.* (1) The statement "Mild stimulant to overcome drowsiness", is unacceptable because there is no evidence to prove that an OTC decongestant could overcome drowsiness caused by antihistamine.

(2) Reference to "fast" or "prompt" onset of relief is unacceptable for oral products because this action does not occur and is a claim allowed only for topical products.

c. *Topical or oral nasal decongestants.* (1) Reference to effect on "local congestion" is unacceptable since this may be confused with congestion in the bronchioles and chest.

(2) Reference to "extra-strength", the "most effective", "improved remedy" are unacceptable because they suggest the product is particularly effective. All Category I ingredients have been judged effective but no acceptable controlled studies were submitted to the Panel documenting one preparation as more effective than another.

(3) Reference to "used by" or "most recommended by doctors or scientists" is unacceptable because it is difficult to substantiate.

(4) "Checks irritation caused by cold virus" is unacceptable because it implies a curative action rather than symptom-relieving.

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel concludes adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed ingredients and conditions listed below. The Panel believes it reasonable to provide 3 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within 3 years, however, the conditions listed in this category should no longer be marketed in over-the-counter nasal decongestant products. Effectiveness as a nasal decongestant must be demonstrated by determining the ability of a drug to reduce nasal obstruction in patients with acute or chronic rhinitis.

Category III Active Ingredients

The Panel concludes that the available data are insufficient to permit final classification of the following claimed nasal decongestant active ingredients:

Beechwood creosote
Bornyl acetate (topical)
Camphor (topical/inhalant)
Cedar leaf oil (topical)
1-Desoxyephedrine (inhalant)
Ephedrine preparations (oral): Ephedrine, Ephedrine hydrochloride, Ephedrine sulfate, Racephedrine hydrochloride
Eucalyptol/eucalyptus oil (topical/inhalant)
Menthol/peppermint oil (topical/inhalant)
Phenylpropanolamine hydrochloride (topical)
Thenyldiamine hydrochloride (topical)
Thymol (inhalant)
Turpentine oil (spirits of turpentine) (topical/inhalant)

a. *Beechwood creosote.* The Panel concludes that beechwood creosote is safe in the dosage ranges used as a nasal decongestant but there are insufficient data to permit final classification of its effectiveness for OTC use as a nasal decongestant.

(1) *Safety.* Clinical experience has confirmed that beechwood creosote in the usual dosages contained in lozenges or cough mixtures for nasal decongestant activity is safe.

Creosote is a distillate of wood tar and has a smoky color and a pungent taste. Dosages in excess of 4 gm 3 times daily produces giddiness, dimness of vision, circulatory collapse, convulsions and coma (Ref. 1). Because of the taste, it is normally given well-diluted (Ref. 2). Occasional adverse gastrointestinal side effects are mentioned in one report but are poorly documented (Ref. 3). Based on the available data and the presence of beechwood creosote on the market for many years, the Panel concludes that this ingredient is safe for OTC use.

(2) *Effectiveness.* Except for a recent submission (Ref. 4), there have been no well-controlled studies documenting the effectiveness of beechwood creosote alone or in combination as a nasal decongestant. A single study is reported dealing with nasal airway resistance in 66 patients with degrees of the "common cold." These patients were studied by objective techniques and this study showed significant reduction in nasal resistance for beechwood creosote combination as compared with a placebo 2 hours following administration. Subjective studies with respect to runny nose should note significant changes from the placebo. It is stated that the investigator global evaluations were too small in number to permit statistical interpretation. In reviewing this study it is difficult for the Panel to interpret these statistical analyses which appear to be cumbersome and confusing. In addition, since no dosage information is supplied, the Panel questions the acceptability of the study.

According to the standard compendia (Refs. 1 and 5), an average dosage of beechwood creosote is 250 mg 3 or 4 times daily. In the two submissions to the Panel listing creosote, the dosages are 3.29 mg/lozenge and 33 mg/15 ml every 3 hours (Refs. 6). This 40- to 80-fold difference in dose (3.29 mg/lozenge, 8 doses/day) appears illogical and there is no evidence to indicate that creosote is effective in such low doses. The Panel concludes that further studies are needed to determine effectiveness.

(3) *Proposed dosage.* Adult oral dosage is 250 mg every 4 to 6 hours not to exceed 1500 mg in 24 hours. Children 6 to under 12 years oral dosage is 125 mg every 4 to 6 hours not to exceed 750 mg in 24 hours. Children 2 to under 6 years oral dosage is 62.5 mg every 4 to 6 hours not to exceed 375 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling).

(5) *Evaluation.* Data to demonstrate effectiveness as a nasal decongestant will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part IV. para-

graph C. below—Data Required for Evaluation.)

REFERENCES

(1) "The United States Dispensatory and Physicians' Pharmacology," 26th Ed., Edited by Osol, A., R. Pratt and M. D. Altschule, J. B. Lippincott Co., Philadelphia, p. 341, 1967.
(2) "Drill's Pharmacology in Medicine," 2d Ed., Edited by DiPalma, J. R., McGraw-Hill Co., New York, p. 690, 1958.
(3) Stevens, M. E., A. K. Ronan, T. S. Sourkes and E. M. Boyd, "On the Expectorant Action of Creosote and the Guaiacols," *Canadian Medical Association Journal*, 48:124–127, 1943.
(4) OTC Volume 040289.
(5) "The National Formulary," 7th Ed., American Pharmaceutical Association, Washington, D.C., pp. 105–106, 1942.
(6) OTC Volume 040208 and 040235.

b. *Bornyl acetate (topical)*. The Panel concludes that bornyl acetate is safe in the dose ranges used when applied topically but there are insufficient data to permit final classification of its effectiveness for topical OTC use as a nasal decongestant.

(1) *Safety*. Clinical experience has apparently confirmed that bornyl acetate (topical) is safe in the dosage ranges used as a nasal decongestant. There are no studies to substantiate its safety. The Merck Index (Ref. 1) states that this compound may cause nausea and vomiting, mental confusion, dizziness and convulsions. The dose is not given. The amount present in a commercially available inhaler is not given (Ref. 2). It is one of several aromatic substances in the inhaler.

(2) *Effectiveness*. There are no well-controlled studies documenting the effectiveness of bornyl acetate (topical) as a nasal decongestant. In a report (Ref. 3), bornyl acetate was one of eleven aromatic substances evaluated as nasal decongestants. Patients presumably with nasal congestion were used. Nasal resistance was measured before treatment and at 5, 15, 30, 60, 90 and 120 minutes after treatment. Bornyl acetate 112.5 mg was impregnated on a cotton wick through which air was forced and the patient inhaled. In the morning, 50 cc of air was administered in each nostril and 150 cc in each nostril in the afternoon. In 11 patients, there was a statistically significant decrease in the nasal resistance at the higher dose. This was not a well designed study.

(3) *Proposed dosage*. The Panel is unable to determine a proposed dosage. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

(4) *Labeling*. The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation*. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

REFERENCES

(1) "The Merck Index," 8th Ed., Merck and Company, Inc., Rahway, New Jersey, p. 160, 1968.
(2) OTC Volume 040065.
(3) Grubb, T. C., "The Nasal Decongestant Effect of Aromatic Substances," Draft of unpublished study is included in OTC Volume 040298.

c. *Camphor (topical/inhalant)*. The Panel concludes that camphor is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical/inhalant OTC use as a nasal decongestant.

(1) *Safety*. Clinical experience has confirmed that camphor (tropical/inhalant) is safe in the dosage ranges used as a nasal decongestant.

Camphor is a local irritant producing skin redness when rubbed on the skin. However, when not vigorously applied, it may produce a feeling of coolness on the skin as does menthol. It acts similarly on the respiratory tract. Taken orally in small doses it produces a feeling of warmth and comfort in the stomach but in larger doses it is irritating and can cause nausea and vomiting. Camphor also has a mild local anesthetic action and its application to the skin may be followed by numbness. The systemic effects are primarily related to stimulation of the central nervous system. The ingestion of solid camphor by children can cause convulsions (Ref. 1). As little as 0.75 gm of camphor equivalent to a teaspoonful of liniment of camphor or camphorated oil which contains 20 percent camphor has been fatal to a child. Commercially available ointments containing mixtures of volatile substances for use as decongestants or antitussives contain about 5 percent camphor. Since it is conceivable that ingestion of a sufficient amount of such a preparation could produce toxic effects in a young child, a suitable warning should be present on the label. The ingestion of 2 gm of camphor generally produces toxic effects in an adult although up to 1.5 oz has been ingested with recovery (Ref. 2).

(2) *Effectiveness*. There are no well-controlled studies documenting the effectiveness of camphor (topical/inhalant) as a nasal decongestant. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

Using an electronic technique for measuring nasal airflow in infants and children, Noller reported that following application of a camphor-containing ointment to the nasal passageway resulted in an initial reduction in airflow followed by an increase in airflow over the pretreatment level. The study report did not, however, indicate the concentration of camphor applied nor were data supplied in the report (Ref. 3). Other studies involving the objective measurement of the nasal decongestant activity of camphor utilized mixtures of volatile substances in topically applied ointments (Refs. 4 through 6) and in steam inhalations (Ref. 7). In these studies, although significant nasal decongestion compared to placebo has been demonstrated, it is not evident whether the camphor component contributed to this effect.

(3) *Proposed dosage*. Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 5 percent ointment preparation: To be rubbed on the throat, chest and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapor rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 7 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in any hot steam vaporizer, bowl or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 0.2 to 15 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling*. The Panel recommends the Category I labeling for topical nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: Warning "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: Warning: "For steam inhalation only. Do not take by mouth".

(5) *Evaluation*. The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation).

(iii) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation).

REFERENCES

(1) Swinyard, E. A. "Demulcents, Emollients, Protectives and Absorbents, Antiperspirants and Deodorants, Absorbable Hemostatics, Astringents, Irritants, Sclerosing Agents, Caustics, Keratolytics, Antiseborrheics, Melanizing and Demelanizing Agents, Mucolytics, and Certain Enzymes," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman,

The MacMillan Co., New York, p. 993, 1970.
(2) Thienes, C. H. and T. J. Haley, "Clinical Toxicology of Commercial Products," 3d Ed., Lea and Febiger, Philadelphia, pp. 24–25, 1955.
(3) Nolier, H. G., "Electronic Measurements on the Nasal Mucous Membrane During Exposure to Menthol," (English translation), ("Elektronische Messungen an der Nasenschleimhaut unter Methol-wirkung"), *in* "Menthol and Menthol-containing External Remedies," Edited by Dost, F. H. and B. Leiber, Georg Thieme Verlag, Stuttgart, Germany, pp. 146–153, 1966.
(4) Blanchard, C. L., S. J. Borsanyi and T. C. Grubb, "Evaluation of Nasal Decongestant Drugs," *The Eye, Ear, Nose and Throat Monthly*, 43:76–82, 1964.
(5) Stamos, E., "Vaporub. Nasal Decongestant Study: Vick Rhinorrheometer. CRD 71–1," Draft of unpublished data is included in OTC Volume 040298.
(6) Carter, V. H., "Vaporub. Nasal Decongestant Study: Vick Rhinorrheometer. CRD 72–7," Draft of unpublished data is included in OTC Volume 040298.
(7) Ciampi, L. A., "Vaposteam. Nasal Decongestant Vick Rhinorrheometer. CRD 71–5," Draft of unpublished data is included in OTC Volume 040298.

d. *Cedar leaf oil (topical)*. The Panel concludes that cedar leaf oil is safe in the dosage ranges used when applied topically but there are insufficient data to permit final classification of its effectiveness for topical OTC use as a nasal decongestant.

(1) *Safety*. Clinical experience has confirmed that cedar leaf oil (topical) is safe in the dosage ranges used as a nasal decongestant.

Cedar leaf oil is the volatile oil steam distilled from the fresh leaves of Thuja occidentialis. The oil is reputed to be ecbolic but abortions cannot be induced with safe doses. The actions are like turpentine but the toxicity greater. In most cases oral ingestion of a teaspoonful may cause illness in an adult and less than 1 oz may be lethal (Refs. 1 and 2).

Several studies support the safety of a topically applied mixture of volatile oils, 16 percent weight/weight, in petrolatum. Although this mixture contains cedar leaf oil, the concentration of individual ingredients is not specified (Ref. 3).

(2) *Effectiveness*. There are no well-controlled studies documenting the effectiveness of cedar leaf oil (topical) as a nasal decongestant. Cedar leaf oil by inhalation is probably transiently effective as a nasal decongestant.

In a study of 10 patients with head colds, not double-blind or placebo-controlled, inhalation of a measured volume of cedar leaf oil vapors induced a significant nasal decongestant effect persisting for 30 minutes as measured by anterior rhinometry. Increasing the volume of inhaled vapors intensified but did not prolong the decrease in nasal resistance (Ref. 4).

In a placebo-controlled crossover study of 36 patients with head colds, application to the chest of a 16 percent weight/weight mixture of volatile oils in petrolatum containing cedar leaf oil demonstrated an apparently significant decrease in nasal resistance compared to the petrolatum control over a 4 hour observation period. The concentration of the cedar leaf oil was not specified. A similar study in 20 additional patients resulted in control and treatment data with overlapping standard errors (Ref. 4). Other studies involving the objective measurements of the nasal decongestant activity of cedar leaf oil utilized mixtures of volatile substances in topically applied ointments (Refs. 5 through 7) and in steam inhalations (Ref. 8). In these studies, although significant nasal decongestion compared to placebo was demonstrated, it was not evident whether the cedar leaf oil component contributed to this effect.

(3) *Proposed dosage*. The Panel is unable to determine a proposed dosage. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

(4) *Labeling*. The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling).

(5) *Evaluation*. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation).

REFERENCES

(1) "Clinical Toxicology of Commercial Products. Acute Poisoning," 3d Ed., Edited by Gleason, M. N., R. E. Gosselin, H. C. Hodge and R. P. Smith, The Williams and Wilkins Co., Baltimore, p. 65, 1969.
(2) "The Dispensatory of the United States of America," 25th Ed., Edited by Osol, A. and G. E. Farrar, Jr., J. B. Lippincott, Philadelphia, p. 1901, 1960.
(3) OTC Volume 040057.
(4) Grubb, T. C., "The Nasal Decongestant Effect of Aromatic Substances," Draft of unpublished study is included in OTC Volume 040298.
(5) Blanchard, C. L., S. J. Borsany and T. C. Grubb, "Evaluation of Nasal Decongestant Drugs," *The Eye, Ear, Nose and Throat Monthly*, 43:76–82, 1964.
(6) Stamos, E., "Vaporub. Nasal Decongestant Study: Vick Rhinorrheometer. CRD 71–1" Draft of unpublished data included in OTC Volume 040298.
(7) Carter, V. H., "Vaporub. Nasal Decongestant Study: Vick Rhinorrheometer. CRD 72–7," Draft of unpublished data is included in OTC Volume 040298.
(8) Ciampi, L. A., "Vaposteam. Nasal Decongestant Vick Rhinorrheometer. CRD 71–4," Draft of unpublished data is included in OTC Volume 040298.

e. *1-Desoxyephedrine (inhalant)*. The Panel concludes that 1-desoxyephedrine is safe in dosage ranges used when used as an inhalant but there are insufficient data to permit final classification of its effectiveness for inhalant OTC use as a nasal decongestant.

(1) *Safety*. Clinical experience has confirmed that 1-desoxyephedrine (inhalant) is safe in the dosage ranges used as a nasal decongestant.

Aqueous nose drops and aqueous spray in concentrations up to 1 percent caused burning, stinging, rhinorrhea and sneezing in up to 21.5 percent of subjects. Palpitations were rare (Ref. 1). With oral doses of 50 to 100 mg two of ten subjects had transient dizziness and nervousness but no blood pressure changes were seen (Ref. 2). No untoward effects of an oral dose of 25 mg 3 times daily for up to 28 days were observed in eight patients (Ref. 2).

(2) *Effectiveness*. There are no well-controlled studies documenting the effectiveness of 1-desoxyephedrine as a nasal decongestant. The effectiveness is therefore uncertain, as data are conflicting and properly controlled objective studies have not been presented.

Uncontrolled studies using nasal drops, 0.25 percent to 1.0 percent concentration, suggest that nasal mucous membrane constriction does occur at the higher concentrations (Ref. 1). An uncontrolled subjective study using an inhaler in 100 patients showed relief of nasal obstruction in 89 percent of cases. Onset of relief was usually in 1 minute and lasted up to 4 hours (Ref. 3). In another similar study duration of relief varied from ½ to 2 hours (Ref. 4). Two double-blind studies of inhalers containing aromatic oils with and without 1-desoxyephedrine showed no differences in nasal airflow studies using the Butler-Ivy technique (Refs. 5 and 6). However, one study (Ref. 6) showed that the inhalers with or without 1-desoxyephedrine were more effective than a placebo inhaler. This suggests the possibility that at least part of the effectiveness of the inhaler might be due to the aromatic oils. Some improvement for less than 30 minutes in airway resistance was shown for camphor, menthol, and bornyl acetate (Ref. 7).

Two single-blind studies comparing an inhaler containing aromatic oils and 1-desoxyephedrine, an inhaler containing only 1-desoxyephedrine, and a placebo inhaler were done using nasal airway resistance measured by a rhinorrheometer (Refs. 8 and 9). Both studies showed that the inhaler with aromatic oils and 1-desoxyephedrine was better than the inhaler containing only 1-desoxyephedrine and both were better than the placebo. Activity was maintained for at least 30 minutes with a maximum at 5 minutes but for less than 60 minutes. These studies suggest that 1-desoxyephedrine has some transient nasal vasoconstrictor effect.

In a recent double-blind, noncrossover, subjective rhinoscopic study of 100 male patients both the drug containing inhaler and placebo inhaler gave significant subjective effect for up to 60 minutes (Ref. 10). Slight rhinoscopic improvement was present in both groups. However, the drug containing inhaler groups, when compared with placebo had significantly greater subjective relief and greater improvement in rhinoscopic parameters.

The above review suggests that 1-desoxyephedrine probably has a nasal vasoconstrictor effect which is relatively brief. However, to be certain of effectiveness, double-blind studies with objective measurements of nasal airway resistance are required. These studies should also provide information as to rebound congestion with repeated nasal use.

(3) *Proposed dosage.* Adult inhalant dosage from an inhaler that shall deliver in each 800 ml air 40 to 150 mcgm l-desoxyephedrine is 2 inhalations in each nostril not more frequently than every 2 hours. Children 6 to under 12 years inhalant dosage from an inhaler that shall deliver in each 800 ml air 40 to 150 mcgm l-desoxyephedrine is 1 inhalation in each nostril not more frequently than every 2 hours. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients (See part VIII. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required from one additional objective nasal airway resistance study in patients with nasal congestion due to acute rhinitis in accordance with the guidelines set forth below for nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

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(1) Fabricant, N. D. et al., "Clinical Evaluation," Draft of unpublished data is included in OTC Volume 040298.

(2) Batterman, R. C., "Studies with Levodesoxyephedrine," Draft of unpublished data is included in OTC Volume 040298.

(3) Greenberg, L., "Resume of Clinical Study of 1-Desoxyephedrine Inhaler," Draft of unpublished data is included in OTC Volume 040298.

(4) Memo to Moore, H. L. from J. S. Scanlan, "Improved Inhaler," is included in OTC Volume 040298.

(5) Memo to Scanlan, J. S. from W. E. Burke, "Current Domestic Inhaler—Clinical Evaluation," is included in OTC Volume 040298.

(6) Sanford, T., "Inhaler," Draft of unpublished data is included in OTC Volume 040298.

(7) Grubb, T. C., "The Nasal Decongestant Effect of Aromatic Substances," Draft of unpublished data is included in OTC Volume 040298.

(8) Mendoza, J. A., "Vick Inhaler," Draft of unpublished data is included in OTC Volume 040298.

(9) Turgeon, R. F., "Vick Inhaler," Draft of unpublished data is included in OTC Volume 040298.

(10) OTC Volume 040231.

f. *Ephedrine preparations (ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine hydrochloride) (oral).* The Panel concludes that ephedrine and its salts are safe in the dosage ranges used orally but there are insufficient data to permit final classification of their effectiveness for oral OTC use as nasal decongestants.

(1) *Safety.* Clinical experience has confirmed that ephedrine and its salts (oral) are safe in the dosage ranges used as a nasal decongestant.

Ephedrine has both central and peripheral effects when absorbed systemically and stimulates, directly or indirectly, both alpha and beta receptors (Ref. 1). In clinical usage the central effects are stimulatory and include tenseness, nervousness, tremor and sleeplessness. Peripheral effects include bronchodilation, and possible shrinkage of mucous membranes (decongestion) although this has not been documented. Other peripheral effects include awareness of heartbeat and tachycardia accompanied usually by some elevation of blood pressure, both systolic and diastolic. The cardiovascular and central effects set limits on dosage, limits which vary widely among patients as judged by clinical experience. Anorexia and nausea also occur in some patients. Difficulty in urination may occur in older males with prostatic hypertrophy. Overdosage results in exaggeration of the side effects which patients describe as disagreeable and can usually be depended upon to prevent overuse or abuse. Ordinary doses may cause marked and potentially dangerous increases in blood pressure in patients taking monoamine oxidase (MAO) inhibitors.

(2) *Effectiveness.* There are insufficient studies documenting the effectiveness of ephedrine and its salts (oral) as nasal decongestants. One controlled objective measurement study in patients with nasal obstruction demonstrated nasal decongestant effectiveness of orally administered ephedrine sulfate in doses of 25 mg (Ref. 2). No conclusive data were found to support claims of effectiveness for doses 8 to 12 mg contained in OTC submissions.

(3) *Proposed dosage.* Adult oral dosage is 8 to 12 mg not more than every 4 hours not to exceed 72 mg in 24 hours. Children 6 to under 12 years oral dosage is 4 to 6 mg not more than every 4 hours not to exceed 36 mg in 24 hours. Children 2 to under 6 years oral dosage is 2 to 3 mg not more than every 4 hours not to exceed 18 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

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(1) "The Pharmacological Basis of Therapeutics," 3d Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, pp. 505–506, 1965.

(2) McLaurin, J. W., W. F. Shipman and R. Rosedale, "Oral Decongestants," *Laryngoscope,* 71:56–67, 1961.

g. *Eucalyptol/eucalyptus oil (topical/inhalant).* The Panel concludes that eucalyptol/eucalyptus oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as a nasal decongestant.

(1) *Safety.* Clinical experience has confirmed that eucalyptol/eucalyptus oil (topical/inhalant) is safe in the dosage ranges used as a nasal decongestant.

Eucalyptus oil is about 70 percent active eucalyptol. Fatalities have followed doses of the oil as small as 3.5 ml although recovery has occurred after doses of 20 and even 30 ml. Symptoms include epigastric burning with nausea and vomiting, vertigo, ataxia, muscle weakness and stupor (Refs. 1 and 2). A study of 223 subjects in which an ointment containing several volatile substances including eucalyptus oil 1.3 percent was applied for 48 hours to both areas of intact skin under a patch and to abraded skin revealed no instances of irritation, inflammation, wheal or hives following the period of exposure (Ref. 3). A study of 10 subjects who received application of an ointment containing several volatile substances including eucalyptus oil 1.3 percent to their trunks 3 times daily for 3 weeks, then 1 week off followed by another 1 week of treatment, revealed no local reactions during this subsequent challenge phase (Ref. 4). A study of infants and children with respiratory infection who received an ointment containing a mixture of volatile oils including eucalyptus oil 1.3 percent applied to the chest and neck demonstrated no adverse effect from inhaled vapors by that route of administration on the rate of clearing of laryngeal edema (Ref. 5). A liquid mixture of volatile substances including eucalyptus oil 1.7 percent is placed in the water of a hot steam vaporizer and administered via inhalation. Exaggerated use studies in adults and children, i.e., exposure for several hours to higher than recommended exposure concentrations either due to sitting in closer proximity to the vaporizer or placing 2 to 5 times the recommended dose of the volatile substance in the vaporizer, was not associated with irritating or toxic effects (Refs. 6 and 7).

A series of studies assessing buccal safety and overt side effects from lozenges containing a mixture of volatile oils was conducted in over 300 subjects. Lozenges containing up to 5.5 mg eucalyptus oil were dissolved in the mouth every hour for 8 hours on 2 successive days. Mild erythema of the buccal mucosa and tongue was observed but did not differ appreciably from the response to dissolving lozenge sugar base without volatile oils. The incidence of gastrointestinal symptoms did not differ from control either (Refs. 8 through 11).

An aerosolized dosage form of volatile substances including 1 percent eucalyptus oil has also been utilized for treatment of nasal congestion. In humans, such aerosol sprays have been generally safe when used as directed but there have been reports of deaths from deliberate sniffing abuse, particularly when the subject inhales from a plastic bag into which the material has been sprayed (Ref. 12). Furthermore, one commercial preparation containing a particular solvent, 1,1,1-trichloroethane, was recently recalled from the market due to potential hazards of this substance (Ref. 13).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of eucalyptol/eucalyptus oil (topical/inhalant) as a nasal decon-

gestant. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

In a study of nine patients with head colds, which was not double-blinded or placebo controlled, inhalation of 50 ml volume of eucalyptus vapors did not induce a significantly decreased airway resistance as measured by anterior rhinometry. Increasing the inhaled volume to 300 ml of eucalyptus oil vapors did induce a significant decrease in airway resistance for 15 minutes, but this was followed by increased nasal resistance over the next 100 minutes (Ref. 14). Other studies involving objective measurement of nasal decongestant activity of eucalyptus oil involved mixtures of volatile substances topically applied as ointments (Refs. 15 through 17), in steam inhalations (Refs. 18 and 19) and room aerosol sprays (Refs. 20 through 23). In these studies, although significant nasal decongestant activity as compared to placebo was demonstrated, whether the eucalyptus oil component contributed to this effect is not evident.

The effect of rinsing and gargling twice daily with an aqueous mixture of volatile substances on the incidence of colds and the severity of the symptoms associated with colds was evaluated in a long-term double-blind placebo-controlled subjective study in school children. The results of the study revealed milder nasal symptoms and cough symptoms in individuals using the medicated mouthwash as compared to the placebo. Although the medicated mouthwash contained 0.91 mg/ml eucalyptol, the results did not demonstrate the contribution of this component to the overall alleviation of symptoms (Ref. 24).

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 1.3 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 1.7 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation: May be repeated 3 times daily.

(iii) For inhalation use as a 1 percent room spray: Spray room for 15 to 20 seconds in the vicinity of the patient. May be repeated at ½ to 1 hour intervals as needed.

(iv) For topical use as a lozenge 0.2 to 15.0 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

(v) For use as a mouthwash 0.91 mg/ml solution: Gargle with ⅔ oz (20 ml) twice daily.

For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII, paragraph C. below—Data Required for Evaluation.)

(iii) For inhalation use as a room spray: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(iv) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(v) For use as a mouthwash: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

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h. *Menthol/peppermint oil (topical/inhalant).* The Panel concludes that menthol/peppermint oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as a nasal decongestant.

(1) *Safety.* Clinical experience has confirmed that menthol/peppermint oil (topical/inhalant) is safe in the dosage ranges used as a nasal decongestant.

Menthol is the chief constituent of peppermint oil, comprising not less than 50 percent, and may be obtained by distillation of the oil or by synthesis (Ref. 1). Toxic effects with an excess ingestion of peppermint oil or mentholated products can include abdominal pain, nausea, vomiting and symptoms of central nervous system depression such as dizziness, staggering gait, slowed respiration, flushed face, sleepiness and coma (Refs. 2 and 3). The fatal oral dose of menthol itself in man is about 2 gm (Ref. 4). Topically applied menthol produces a cooling sensation presumably due to

stimulation of the cold sensory receptors, whereas higher concentrations have irritant properties. In one study, a 20 percent solution of menthol in oil rubbed on to the skin induced an intense and lasting cooling sensation followed by numbness with slight burning and skin redness. A 0.5 percent solution applied to the nasal or oral mucosa was subjectively irritating whereas a 0.2 percent solution was judged nonirritating (Ref. 5). A study of 223 subjects in which an ointment containing several volatile substances including menthol 2.8 percent was applied for 48 hours to both areas of intact skin under a patch and to abraded skin revealed no instances of inflammation, wheal, hives or primary irritation following the period of exposure (Ref. 6). Repeated topical application of mentholated products has been reported to give rise to hypersensitivity reactions including contact dermatitis (Ref. 4). A study of 10 subjects who received application of an ointment containing several volatile substances including menthol 2.8 percent to their trunks 3 times daily for 3 weeks, then 1 week off followed by another week of treatment, revealed no local reactions during this subsequent challenge phase (Ref. 7). The incidence of hypersensitivity to menthol appears to increase with increased duration of use. For example, one survey revealed an incidence of less than 1 percent menthol hypersensitivity in 542 patients using a mentholated ointment for less than 10 years whereas an incidence of 3.4 percent hypersensitivity was seen in 144 patients using this type of a preparation for longer than 10 years (Ref. 8).

In infants and small children nasal ointment or drops containing menthol may cause spasm of the glottis and cases of dangerous asphyxiation have been reported in infants following local application of menthol. For this reason a warning against the topical application of menthol-containing products directly to the nostrils of infants has been recommended (Refs. 4 and 9). A study of infants and children with respiratory infection who received an ointment containing a mixture of volatile oils including a 2.8 percent menthol applied to the chest and neck demonstrated no adverse effect from the inhaled vapors by that route of administration on the rate of clearing of laryngeal inflammation. In this study 35 children (23 under 2 years of age) with respiratory infection received only standard forms of therapy, e.g., antibiotics and fluids, while 37 children (30 under 2 years of age) received standard therapy plus the mentholated ointment to the chest and neck. Laryngoscopic examination revealed comparable rates of clearing of laryngeal inflammation (Ref. 10).

A liquid mixture of volatile substances including 3.66 percent menthol is placed in the water of a hot steam vaporizer and administered via inhalation. A number of studies involving nearly 900 subjects in which this mixture was administered at recommended doses was not associated with significant complaints of subjectively perceived adverse effects (Refs. 11 through 23). Exaggerated use studies in adults and children, i.e., exposure for several hours to higher than recommended exposure concentrations either due to sitting in closer proximity to the vaporizer or placing 2 to 5 times the recommended dose of the volatile substance in the vaporizer, was not associated with irritating or toxic effects (Refs. 24 and 25).

In two studies involving 40 healthy subjects who were asked to dissolve 2 candy-base lozenges every 20 minutes for 2 hours, each containing 1.36 mg of menthol together with other volatile oils, exhibited no adverse effects with the exception of one report of nausea and vomiting. This was attributed to a dislike for the wild cherry flavor of the lozenge (Refs. 26 and 27). In a group of 70 healthy subjects (50 adults and 20 children, ages 8 to 12), half of the subjects dissolved a menthol-eucalyptus lozenge, 9.62 mg menthol and 5.55 mg eucalyptus oil, every hour for 8 hours on 2 successive days, the other half dissolved the cough drop base without the aromatics. In this intensive dosage schedule, a slightly larger number of subjects demonstrated mild irritation of the oral mucosa on days 1 and 2, but there were no differences between the two groups in the severity of irritation or residual findings after day 2. No systemic complaints were reported (Ref. 28). A similar study using a lozenge formulation containing menthol 8.14 mg and eucalyptus oil 4.625 mg versus a lozenge base without volatile substances produced comparable results (Ref. 29).

An aerosolized dosage form of volatile substances including 1 percent menthol has also been utilized for treatment of nasal congestion and cough symptoms. Rats exposed to acute overdoses of the spray in a confined chamber for 6 hours revealed no untoward behavorial response or airway tissues abnormality upon autopsy examination (Ref. 30). A group of four monkeys were exposed to 200 gm per day of the aerosol, i.e., 2 gm of menthol total dose in divided doses over an 8 hour period for 14 consecutive days in a confined chamber. Eye irritation was the only pharmacotoxic sign observed during the study (Ref. 31). In humans, such aerosol sprays have been generally safe when used as directed but there have been reports of deaths from deliberate sniffing abuse, particularly when the subject inhales from a plastic bag into which the material has been sprayed (Ref. 32). Furthermore, one commercial preparation containing a particular solvent, 1,1,1-trichloroethane, was recently recalled from the market due to potential hazards of this substance (Ref. 33).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of menthol/peppermint oil (topical/inhalant) as a nasal decongestant. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

Menthol has been used in external preparations for its effects in the nasal passages. A decided cooling sensation is noticed when the substance is applied to the skin or to the mucous membrane. A cooling sensation noted in nasal passages is associated with a feeling of decreased nasal congestion. The cooling sensation, however, is not associated with an actual decrease in surface temperature, thus it is not dependent upon nasal constriction but rather appears to result from an influence on sensory nerve endings responsible for cold reception (Ref. 34). Standard texts, in fact, have noted that the feeling of nasal decongestion accompanying menthol vapor action may be an illusion and, in fact, may be accompanied by increased congestion (Ref. 1).

Using an electronic technique for measuring nasal airflow in 18 infants and children, Noller demonstrated that intranasal application of a 2.82 percent mentholated ointment induced a reduction in airflow during the first 20 minutes which was followed by an increase in airflow over the pretreatment level, lasting 1 to 3 hours (Ref. 35). In three children the menthol ointment was applied to the chest and back with one nostril remaining closed throughout the experiment except during measurement. Increased airflow was noted only in the open nostril up to 4 hours after administration, leading to the conclusion that the effect of menthol was due to the inhaled vapors (Ref. 35).

In a study of 50 patients with head colds, 15 of whom also received a petrolatum placebo application, application to the chest of an ointment containing a mixture of volatile substances including 2.8 percent menthol induced a significant degree of nasal decongestion compared to placebo over an 8 hour period as determined by a modified Butler-Ivy procedure (Ref. 36). Two additional objective-measurement placebo-controlled crossover studies involving chest, throat and back application of an ointment containing a mixture of volatile substances including 2.8 percent menthol revealed a significant nasal decongestant effect compared to placebo over an 8 hour period in a total of 90 patients with head colds (Refs. 37 and 38).

A liquid mixture of volatile substances which is to be added to the water in a hot steam vaporizer and administered via inhalation contains menthol 3.66 percent, camphor 7 percent, eucalyptus oil 1.7 percent and tincture of benzoin 5 percent. Two objective-measurement placebo-controlled studies in patients with nasal congestion due to head cold revealed that this liquid containing volatile substances placed in hot water in a dose of 1 tablespoon per quart induced a statistically significant decrease in nasal airway resistance compared to inhalation of steam alone during the period of steam inhalation (Refs. 24 and 39). It was demonstrated that an optimal distance between the subject and the vaporizer to elicit this effect was 4 to 6 feet (Ref. 24).

An aerosolized mixture of volatile substances to be sprayed in the room and containing menthol 1 percent and eucalyptus oil 1 percent has been studied for its nasal decongestant effect by ob-

jective measurement studies. When sprayed into the room for 15 seconds in the vicinity of the subject's head, measurement of expiratory nasal flow rate in 25 head cold patients revealed at least a 20 percent increase in expiratory flow rate in 19 of the patients when compared to pretreatment control readings. No placebo was utilized, however, and since measurements were only made for 6 minutes after drug administration, the average duration of effect was not determined (Ref. 40). In a subsequent study on five patients with head colds, the aerosolized mixture of volatile substances readministered at 0, 2, 4 and 7 hours led to a transient increase in expiratory nasal flow rate over the pretreatment level each time. Duration of this effect following each dose was not determined (Ref. 41). In an objective-measurement placebo-controlled study of 15 patients with head colds, nasal airway resistance was determined following a 20-second placebo aerosol spray and then for 30 minutes after a 20-second spraying of the volatile oil mixture which provided a total of 20 gm of aerosolized material. A significant decrease in nasal airway resistance was obtained with the medicated aerosol compared to placebo in 9 of the 15 subjects, but in only 3 of these subjects did the effect persist throughout the 30-minute period of observation (Ref. 42). A similar study with an additional 15 patients having partial nasal congestion due to head colds revealed comparable results (Ref. 43).

Use of a sensitive gas chromatographic technique has revealed the presence of menthol vapors in air expired through the nasal passage during the time a menthol-containing lozenge was dissolving in the subject's mouth (Ref. 44). Patients with nasal congestion due to head colds were divided into 2 groups of 15 each. One group received a 4.27 gm lozenge containing 0.15 percent menthol and 0.04 percent eucalyptus oil while the other group received a nonmedicated lozenge base. No significant difference in nasal airway resistance between the placebo and active medication group could be demonstrated (Ref. 45). In a subjective evaluation study using allergic rhinitis patients, 78.4 percent of the patients using the menthol-eucalyptol lozenge compared to 65.4 percent of the placebo groups claimed relief of their stuffy nose after 1 day of treatment. The difference between the groups was not, however, statistically significant (Ref. 46).

The effect of rinsing and gargling twice daily with an aqueous mixture of volatile substances on the incidence of colds and the severity of the symptoms associated with colds was evaluated in a long-term double-blind placebo-controlled subjective study in school children. The results of the study revealed milder nasal symptoms and cough symptoms in individuals using the medicated mouthwash as compared to the placebo. Although the medicated mouthwash contained 0.42 mg/ml menthol, the results did not demonstrate the contribution of this component to the overall alleviation of symptoms (Ref. 47).

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 2.8 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 3.66 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For inhalation use as a 1 percent room spray: Spray room for 15 to 20 seconds in the vicinity of the patient. May be repeated at ½ to 1 hour intervals as needed.

(iv) For topical use as a lozenge 1.0 to 10 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

(v) For use as a mouthwash 0.42 mg/ml solution: Gargle with ⅔ oz (20 ml) twice daily.

For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning.* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required from one additional controlled objective measurement study in patients with nasal congestion due to acute rhinitis in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(iii) For inhalation use as a room spray: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(iv) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(v) For use as a mouthwash: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

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i. *Phenylpropanolamine hydrochloride (topical)*. The Panel concludes that phenylpropanolamine hydrochloride is safe in the dosage ranges used when applied topically but there are insufficient data to permit final classification of its effectiveness for topical OTC use as a nasal decongestant.

(1) *Safety.* Clinical experience has confirmed that phenylpropanolamine hydrochloride (topical) is safe in the dosage ranges used as a nasal decongestant. Phenylpropanolamine hydrochloride as 1 to 5 percent aqueous solution administered by drops or intranasal tampon was well tolerated by most patients, although a few complained of transitory stinging (Refs. 1, 2, and 3). Rhinoscopic examination revealed little or no evidence of nasal irritation following prolonged and continuous use of 3 percent phenylpropanolamine nasal solution but details of time parameters of drug administration were not given (Ref. 2). There is a need for additional data relating frequency of use with incidence and intensity of rebound nasal congestion in adults and children.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of phenylpropanolamine hydrochloride (topical) as a nasal decongestant. Its effectiveness is uncertain because no properly controlled objective measurement studies have been presented.

Phenylpropanolamine hydrochloride is generally considered to exert a nasal decongestant effect when topically applied as a 1 to 3 percent solution (Refs. 1 through 5). Administration as drops or soaked intranasal tampons (3 to 5 minutes contact time) to adult chronic rhinitis patients resulted in subjective and rhinoscopic evidence of nasal decongestion persisting up to 2 hours. None of these studies were controlled, double-blind or contained objective measurements in their design. No data from studies in children were presented. Studies of nasal decongestant effectiveness of topical phenylpropanolamine hydrochloride in 0.25 percent to 0.5 percent concentrations are currently in progress and the Panel was told that a report will be submitted when completed (Ref. 6).

(3) *Proposed dosage.* Adults and children above 6 to under 12 years topical dosage is 2 to 3 drops or sprays of a 1 percent solution in each nostril every 2 to 4 hours. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician. Concentrations and frequency of administration for safe and effective use have not been established in children under 6 years.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

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j. *Thenyldiamine hydrochloride (topical)*. The Panel concludes that thenyldiamine hydrochloride is safe in the dosage ranges used when applied topically but there are insufficient data to permit final classification of thenyldiamine hydrochloride as safe and effective for OTC use as a topical nasal decongestant.

(1) *Safety.* Clinical experience has confirmed that thenyldiamine hydrochloride (topical) is safe in the dosage ranges used as a nasal decongestant. Topically, 0.1 percent or 0.2 percent thenyldiamine hydrochloride in combination with phenylephrine hydrochloride, 0.25 and 0.5 percent, produced only "slight" or "moderate" stinging in some of the subjects in human intranasal irritation studies conducted by a manufacturer (Ref. 1). Preparations containing 0.5 percent thenyldiamine hydrochloride produced "moderate" to "severe" stinging in all subjects and irritation of the larynx in a few subjects. There are no data available on the incidence of rebound congestion.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of thenyldiamine hydrochloride (topical) as a nasal decongestant. In a randomized, double-blind, and

crossover study of patients with acute rhinitis, a combination of thenyldiamine hydrochloride, 0.1 percent, with other active ingredients applied intranasally as a sprayed solution produced a subjectively evaluated nasal decongestant effect which was significant as compared to that produced by a placebo solution (Ref. 2). However, in this study the effectiveness of the combination product, thenyldiamine with phenylephrine and benzalkonium, was not significantly different from that of the product minus thenyldiamine. In fact, the nasal decongestant effect produced by phenylephrine alone and the nasal decongestant effect produced by thenyldiamine alone were not significantly different from the nasal decongestant effect produced by the combination commercial product. The three preparations did not differ at the 95 percent confidence level.

In another controlled study to determine the therapeutic contribution of topically applied thenyldiamine in a combination product with phenylephrine and benzalkonium chloride, no additive or synergistic effect was evident over that obtained by phenylephrine 0.5 percent alone, when measured by posterior electronic rhinometry or by a plethysmograph with a face mask (Ref. 3).

The manufacturer's labeling states that thenyldiamine hydrochloride "offsets the results of mediator release to the extent it is producing obstruction and at the same time opposes cholinergic hyperemia and rhinorrhea." Thacker (Ref. 4) supports inclusion of antihistamines in OTC nasal decongestant products to prevent engorgement from migration of excessive body fluids from the vascular system into tissue spaces and to aid in alleviating allergic reactions to ingredients in the solution. This supposition, however, is not supported by scientific evidence.

Studies with topical thenyldiamine indicate it may be a nasal decongestant but no nasal decongestant claims are made for this ingredient in the commercially available OTC products, although the products themselves are nasal decongestants. Present claims made for thenyldiamine are based on topical application of an antihistamine but there are no studies on the antihistamine activity of the drug applied topically.

There are no data on the use of this drug in children.

(3) *Proposed dosage.* Adult topical dosage is 1 to 3 drops or sprays of a 0.1 percent solution in each nostril not more than every 4 hours. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

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(3) Gould, W. J., "Clinical Summary of NTZ Study, MRD, 70-65," Draft of unpublished paper is included in OTC Volume 040298.

(4) Thacker, E. A., "Nasal Solutions with Combined Therapeutic Effects," *The Eye, Ear, Nose and Throat Monthly*, 29:609-613, 1950.

k. *Thymol (topical/inhalant).* The Panel concludes that thymol is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical/inhalant OTC use as a nasal decongestant.

(1) *Safety.* Clinical experience has apparently confirmed that thymol (inhalant) is safe in the dosage ranges used as a nasal decongestant.

Thymol is an alkyl derivative of phenol and has bactericidal, fungicidal, and anthelmintic properties (Ref. 1). When hydrogenated, thymol is converted to the closely related drug, menthol (Ref. 2). The LD_{50} of thymol in mice is 1,800 mg/kg orally (Ref. 3). No data were found bearing on the drug's toxicity in man. In view of thymol's relative inactivity compared to menthol, of which 50 to 120 gm "would have to be absorbed to cause poisoning" (Ref. 4), thymol is presumed to be relatively nontoxic.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of thymol (inhalant) as a nasal decongestant. Experiments in anesthetized rabbits have indicated that thymol administered by steam inhalation augmented the concentration of soluble mucous in the respiratory tract fluid (Ref. 2). The dose administered was unknown but the concentration in the vaporizer was in excess of 81 mg/kg. The volume of secretions did not change. Much lower concentrations of menthol were effective (1 mg/kg). In man no data on effectiveness of thymol alone were found although a mixture containing thymol, menthol, eucalyptol, and propylene glycol appeared to suppress citric acid induced cough (Ref. 5) and to reduce resistance in the nasal and bronchial airways (Ref. 6).

Studies involving the objective measurement of the nasal decongestant activity of thymol were done with mixtures of volatile substances, topically applied as ointments (Refs. 7, 8 and 9), and in steam inhalations (Refs. 10 and 11). Although significant nasal decongestant activity as compared to placebo was demonstrated, it was not evident whether the thymol component contributed to this effect.

The effect of rinsing and gargling twice daily with an aqueous mixture of volatile substances on the incidence of colds and the severity of the symptoms associated with colds was evaluated in a long-term double-blind placebo-controlled subjective study in school children. The results of the study revealed milder nasal symptoms in individuals using the medicated mouthwash as compared to the placebo. Although the medicated mouthwash contained 0.63 mg/ml thymol, the results did not demonstrate the contribution of this component to the overall alleviation of symptoms (Ref. 12).

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 0.1 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 0.13 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For inhalation use as a 0.1 percent room spray: Spray room for 15 to 20 seconds in the vicinity of the patient. May be repeated at ½ to 1 hour intervals as needed.

(iv) For topical use as a lozenge 0.02 to 2.0 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

(v) For use as a mouthwash 0.63 mg/ml solution: Gargle with ⅔ oz (20 ml) twice daily.

For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(iii) For inhalation use as a room spray: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(iv) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(v) For use as a mouthwash: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

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(9) Carter, V. H., "Vaporub. Nasal Decongestant Study—Vick Rhinorrheometer. CRD 72–7," Draft of unpublished data is included in OTC Volume 040298.

(10) Shapiro, M., "Steam Alone vs. Vaposteam in Steam," Draft of unpublished data is included in OTC Volume 040298.

(11) Ciampi, L. A., "Vaposteam. Nasal Decongestant Vick Rhinorrheometer. CRD 75–1," Draft of unpublished data is included in OTC Volume 040298.

(12) OTC Volume 040278.

1. *Turpentine oil (spirits of turpentine) (topical/inhalant).* The Panel concludes that turpentine oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as a nasal decongestant.

(1) *Safety.* Clinical experience has confirmed that turpentine oil (topical/inhalant) is safe in the dosage ranges used as a nasal decongestant.

Oil of turpentine is a volatile oil consisting of a mixture of pinenes derived from the oleoresin obtained from *Pinus palustris*. Nelson et al. (Ref. 1) found exposure to a vapor of 420 to 560 mcg/l acceptable to most of their human subjects. The threshold for industrial exposure for 8 hours has been set at 560 mcg/l. The maximum concentration obtainable with a currently marketed OTC preparation is 36 mcg/l (Refs. 2 and 3). No histological evidence of pulmonary lesions were seen in mice and rats exposed to lethal concentrations of turpentine vapors (Ref. 4). Inhalation of 300 mcg/l of turpentine vapor by mice for 15 minutes did not influence the electrocardiogram, respiratory minute volume, pulmonary airway resistance or compliance (Ref. 5). One study conducted in mice using a mixture of volatile oils, one of which was turpentine, showed a decrease in pulmonary antibacterial activity (Ref. 6). Two other studies showed no change when the mixture was used (Refs. 7 and 8).

In several studies in children and infants suffering from minor breathing discomforts associated with the "common cold" no side effects that were drug related were observed when a medicated steam was administered (Refs. 9 through 13). Turpentine has been widely used as a part of a mixture of volatile oils for many years with approximately two complaints per million packages purchased (Ref. 14).

(2) *Effectiveness.* Studies involving the objective measurement of the nasal decongestant activity of turpentine were done with mixtures of volatile substances, topically applied as ointments (Refs. 15, 16, and 17), and in steam inhalation (Refs. 18 and 19). Although significant nasal decongestant activity as compared to placebo was demonstrated in these studies, it was not evident whether the turpentine contributed to this effect.

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 4.0 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapor rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 5.5 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl, or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

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(17) Carter, V. H., "Vaporub. Nasal Decongestant Study—Vick Rhinorrheometer. CRD 72–7," Draft of unpublished data is included in OTC Volume 040298.

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Category III Labeling

The Panel concludes that the available data are insufficient to permit final

classification of the labeling claims identified below for nasal decongestants. Additional data are required to support the following nasal decongestant claims:

Reference to "preventing sneezing", "drying runny nose" or "checking post nasal drip" are unsubstantiated claims for nasal decongestants unless studies specifically designed to assess these activities are presented. Studies of nasal decongestants have assessed the effect on nasal airway resistance or the ease of breathing but not the effect on rhinorrhea.

Reference to an indirect effect in "preventing or alleviating cough" by an effect on nasal congestion is an unsubstantiated claim unless studies specifically designed to assess this activity are presented.

Reference to an effect "to reduce sinus pressure" is an unsubstantiated claim since studies of nasal decongestant activity assess the effect on nasal airway resistance. Although it is assumed that this effect on the nasal mucosa may indirectly facilitate sinus drainage and thus decrease sinus congestion, it would be unsubstantiated to claim a drug effect to decrease sinus pressure without evidence to support this claim.

Reference to the extent of the penetration of topically applied nasal decongestants is unsubstantiated without specific studies to demonstrate the extent of penetration (depth of penetration into the nasal cavity and/or the extent of penetration into the nasal mucosa).

Pressure within the antrum can be measured and recorded in terms of centimeter of water compared to ambient pressure by means of a suitable needle or small trocar placed in the antrum under topical anesthesia. This would be performed in a small number of patients (5 to 10) with nasal congestion associated with an acute respiratory infection who complain of localized headache and/or tenderness in the sinus areas. These pressure measurements would be repeated following the administration of the test preparation or placebo in the dosage range and time intervals recommended for OTC usage. Subjective symptoms such as headache, tenderness, etc., could be evaluated in conjunction with the pressure measurements.

C. DATA REQUIRED FOR EVALUATION

The Panel has agreed that the protocols recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. *Principles in the design of an experimental protocol for testing nasal decongestant drugs.* a. *General principles.* The effectiveness of a nasal decongestant drug should be determined by its ability to reduce nasal obstruction in patients with acute or chronic rhinitis. Tests should involve double-blind placebo-controlled assessment of the drug's ability to decrease nasal airway resistance. Patient-reported subjective assessment is also desirable. The drugs used should be the same as in the OTC preparation and should be given in the same dosage as the recommended label instructions for the preparation. Since either oral or topical nasal decongestants may be administered repeatedly during episodes of nasal congestion, studies should bear on the appropriate interval for dosing to maintain optimal relief of symptoms. For locally applied nasal decongestants, wherein rebound congestion with repeated use is a concern, labeling should specify short-term use in providing temporary relief of nasal congestion. Specific data on this matter should be obtained by testing the topical nasal decongestant in the concentrations and maximal dosage frequencies to be recommended for periods of at least 1 week in order to assess the incidence and severity of a drug-induced increase in nasal airway resistance.

b. *Selection of patients.* Selection of patients for testing should be based on the diagnosis of rhinitis with nasal congestion. Patients with chronic allergic or vasomotor rhinitis present relatively stable nasal congestion and consequently can serve as their own controls in a crossover study design. Patients with acute allergic or infectious rhinitis also represent a large proportion of the patient type likely to self-medicate with a nasal decongestant. Because of the relatively brief time course of these acute disorders and greater variation in stability of congestion, larger numbers of these patients would have to be studied by assigning them in random fashion to placebo or drug groups. Further, for comparative purposes these groups have to be matched by age, sex, and if possible, the degree of nasal congestion at the time of study. Smoking by test subjects should be prohibited 24 hours prior to and during the test.

c. *Methods of study.* Observation should include both the subjective response and objectively measured nasal airway resistance before the drug or placebo is administered, and at appropriate intervals thereafter to demonstrate time of onset, magnitude, and duration of response.

d. *Interpretation of data.* A recommended dose of the test drug should induce a statistically significant reduction in nasal airway resistance when compared with the placebo response.

Evidence of drug effectiveness is required from a minimum of two positive studies based on the results of two different investigators or laboratories.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

e. *Evaluation of safety.* Tests of safety should involve the usual tests for toxicity relevant to the known possible adverse effects of the drugs under testing. Tests should be done in the form of dose response curves up to a maximum therapeutic effectiveness.

IX. MISCELLANEOUS INGREDIENTS

A. GENERAL COMMENT

The action of several drugs considered by the Panel do not fall within the main pharmacologic groups, i.e., antitussives, expectorants, bronchodilators, anticholinergics, antihistamines, and nasal decongestants reviewed by the Panel. However, these miscellaneous ingredients are found in many OTC CCABA products. Because of the differences in their intended action in CCABA products, they are discussed individually below.

B. CATEGORIZATION OF DATA

The miscellaneous ingredients and/or labeling have been reviewed and classified as follows:

1. *Conditions under which CCABA products are not generally recognized as safe and effective or are misbranded.* The use of certain conditions are unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel concludes that the following ingredients and/or labeling should be removed from the market until scientific testing supports their use.

a. *Antihistamines in combination CCABA products exclusively for sedation.* The Panel concludes that the combining of an antihistamine in a CCABA combination product for the exclusive purpose of sedation is irrational. The Panel is aware that CCABA combination products are currently available for use at bedtime and promoted for such various claims as "for restful sleep". However, the duration of drug effects in "nighttime cold preparations" which are recommended to be taken once at bedtime is not fully documented. Although antihistamines produce sedation as a side effect depending upon the dosage, the addition of an antihistamine for the primary purpose of sedation is not rational. The Panel has recommended the use of antihistamines in CCABA combination products only for the relief of symptoms of allergic rhinitis. (See part II. paragraph C.5.b. above—Combination products containing antihistamines with sleep-aid claims.)

Certain antihistamines are generally considered safe for OTC use. The Panel has recommended specific doses for each of these antihistamines after a consideration of the scientific data available for these ingredients. The Panel concluded that the antihistamines reviewed by the Panel and classified as Category I are both safe and effective for the treatment of the symptoms of allergic rhinitis when administered as labeled. (See part VII. paragraph B.1. above—Category I conditions under which antihistamine ingredients are generally recognized as safe and effective and are not misbranded.) However, the Panel does not recommend the addition of another antihistamine to a CCABA combination product for the exclusive purpose of sedation. The rationale for the use of an additional antihistamine in CCABA combination products for the exclusive purpose of sedation has not been demonstrated.

b. *Vitamins used alone or in combination CCABA products with labeling claims for the prevention or treatment of the "common cold".* The Panel is unaware of any well-controlled studies documenting the safety or effectiveness

of vitamins for use in the prevention or treatment of the "common cold". In addition, the Panel concludes that the use of any vitamin in CCABA combination products for the prevention of colds is irrational since such products should only be used when the symptoms of the "common cold" are present. It would, therefore, be irrational for a consumer to take a cold combination product containing vitamins to prevent a cold. The Panel has discussed this issue earlier in this document. (See part II. paragraph C.5.a. above—Combination products containing vitamins.)

The Panel is aware of the popular use of vitamin C for treatment of the symptoms of the "common cold." However, the Panel has reviewed the available data which is discussed below and concludes that no drug labeling claims should be made for vitamin C for the prevention or treatment of the symptoms of the "common cold" until adequate data are available to substantiate such claims. (See part IX. paragraph B.2.b. below—Ascorbic acid (vitamin C).)

2. *Conditions for which the available data are insufficient to permit final classification at this time.* The Panel concludes that adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed active ingredients for the conditions listed below. The Panel believes it reasonable to provide 3 years for vitamin C, 2 years for phenobarbital and caffeine, and 3 years for antihistamines for the development and review of evidence to substantiate the conditions specified below. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within the time period provided, the ingredients listed in this category should no longer be marketed as over-the-counter products. The ingredients considered in this category are:

Antihistamines in combination CCABA products with sleep-aid claims

Ascorbic acid (vitamin C)
Caffeine
Phenobarbital

a. *Antihistamines in combination CCABA products with sleep-aid claims.* The Panel concludes that there are insufficient data to permit final classification of the safety and effectiveness for OTC use of sleep-aid claims for antihistamines in combination CCABA products in which their primary claim is for the relief of the symptoms of allergic disorders. The Panel is aware that antihistamines may have several activities, e.g., antitussive, antihistamine or sedative activity, depending on the dosage level used. The Panel has discussed this issue earlier in this document. (See part II. paragraph C.5.b. above—Combination products containing antihistamines with sleep-aid claims.)

(1) *Safety.* Clinical experience has confirmed that antihistamines are safe in the dosage ranges used in combination CCABA products with sleep-aid claims.

The Panel concludes that the antihistamines reviewed by the Panel and classified as Category I are both safe and effective for the treatment of the symptoms of allergic rhinitis when administered as labeled. (See part VII. paragraph B.1. above—Category I conditions under which antihistamine ingredients are generally recognized as safe and effective and are not misbranded.) However, the Panel was unable to make a final definition as to the safe and effective use of antihistamines as sleep-aids in CCABA products.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of antihistamines in combination CCABA products as sleep-aids. Although sedation may be a side effect, the effectiveness of antihistamines in CCABA combination products as sleep-aids, is not fully understood.

(3) *Proposed dosage.* The Panel is unable to determine a proposed dosage. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

(4) *Labeling.* The Panel recommends that labeling claims contained in each drug manufacturer's currently marketed product, i.e., "for restful sleep", should be used.

(5) *Evaluation.* Data to demonstrate effectiveness will be required to be completed in 3 years. The Panel recommends a testing protocol in conformance with the requirements specified by the OTC Sedative, Tranquilizer and Sleep-Aid Drug Products Panel as published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292).

b. *Ascorbic acid (vitamin C).* The Panel concludes that there are insufficient data to permit final classification of ascorbic acid as safe and effective for OTC use in the prevention or treatment of the "common cold." The use of vitamin C in CCABA combination products has been discussed earlier in this document. (See part II. paragraph C.5.a. above—Combination products containing vitamins.)

(1) *Safety.* Long experience and innumerable studies attest to the fact that ascorbic acid, in doses preventing scurvy, is entirely safe. The daily requirement of ascorbic acid for the adult man is 30 mg and the National Academy of Sciences-National Research Council has therefore set the daily dietary allowance for ascorbic acid at 45 mg (Ref. 1). Ascorbic acid is probably safe in the dosage used for the treatment of acute catarrhal conditions of the nasal mucous membranes which is usually accompanied with profuse discharge from the nostrils, referred to as coryza. Dosages recommended for prevention or treatment of coryza range from 1 to 3 gm or more daily raising blood levels above the renal threshold with consequent rapid excretion by the kidney. Change from a high to a low level of ascorbic acid in the diet appears to predispose to the development of scurvy (Ref. 2).

In humans, massive doses of vitamin C, from 1 to 10 or more gm per day, have not caused toxic symptoms. Diarrhea is the only symptom reported. High levels of urinary ascorbic acid may give false positive tests for sugar in diabetic patients (Ref. 3). Also, theoretically, large doses of ascorbic acid increase the level of uric and oxalic acid in the urine, a possible hazard in patients with a tendency to gout or oxalate renal stones (Ref. 2). Large doses of vitamin C in laboratory animals have been reported to reduce fertility (Ref. 3). In a large study in human subjects (Ref. 4) the administration of large daily doses of vitamin C caused a marked but transitory fall in the vitamin C content of the blood when the vitamin C was discontinued.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of vitamin C in the prevention or treatment of the "common cold."

Ten or more studies have left the matter of effectiveness in doubt. None of the studies done to date have shown ascorbic acid in any of the dosage schedules used to be unequivocally effective, although trends in favor of effectiveness have been seen. The need for elimination of bias by careful design of clinical trials has been repeatedly stressed.

The claimed effects of large doses of vitamin C on the "common cold" include prevention of colds, more rapid recovery and reduced severity.

In reviews of the data, Pauling argued persuasively (Refs. 5 through 8) that the data favored a beneficial effect of large dosages of vitamin C in treating the "common cold." In another review of these data more caution is urged in accepting this interpretation (Ref. 3). In a third review (Ref. 9), data presented by the reviewer as well as data from many other studies are interpreted as favoring a beneficial effect of large dosages of vitamin C in treating the "common cold." However, an addendum citing data published in 1974 (Ref. 10) failed to support a beneficial effect in doses ranging from 50 to 1,000 mg of vitamin C daily.

In a double-blind study comprising 1,000 subjects (Ref. 11) receiving a placebo or vitamin C in a dose of 1,000 mg daily and 4,000 mg for each of the first 3 days of a cold, there were 30 percent fewer days of confinement to the house among those receiving vitamin C as compared with those receiving the placebo, a finding that was highly significant ($p=0.001$). A second study indicated that the effect observed was not ascribable to either a prophylactic or a therapeutic effect alone (Ref. 4). A dosage level of 2,000 mg/day was not significantly different in its effects from one of 250 mg/day.

In the third of a series of large-scale double-blind studies on the effect of vitamin C on the "common cold" also recently published, the data indicated that subjects receiving vitamin C either in regular or sustained release forms in a dose of 500 mg each week, 1,500 mg on the first day of a cold and 1,000 mg daily for the next 4 days, had a significantly

milder illness than those receiving a placebo (Ref. 12). These findings indicate that very large daily doses of vitamin C may be unnecessary.

In a recent study (Ref. 13), a random sample of employees in the National Institutes of Health comprising 190 subjects were given prophylactic daily ascorbic acid (3,000 mg) or a placebo and with the onset of a "cold" were given 3,000 mg or 6,000 mg ascorbic acid or a placebo. The study was well-designed with the exception that the placebo differed in taste from the active drug thus leading the investigators to question whether the observed result of "minor influence on the duration and severity of colds" was attributable to this flaw in the study design rather than to a beneficial effect of ascorbic acid.

One means by which vitamin C might favorably influence the "common cold" is suggested by recent in vitro studies showing that in the presence of 250 mcg/ml vitamin C and glutathione, the growth of one of the causes of the "common cold," rhinovirus, was markedly suppressed. This concentration of vitamin C was without an adverse effect on the cells (Ref. 14). In contrast to the implication that vitamin C has a specific antiviral effect, one of the recent clinical studies indicates that vitamin C has a beneficial effect on various types of illnesses and not only the syndrome referred to as the "common cold" (Ref. 11).

The Panel concludes that the published data support a beneficial effect of vitamin C on the severity and perhaps frequency of the "common cold" when given in dosages exceeding the daily requirement. However, it is not yet clear that this effect is clinically significant. The magnitude of the dosages needed and the optimum schedule for prophylaxis and therapy remain to be determined.

(3) *Proposed dosage.* The Panel is unable to determine a proposed dosage. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing.

(4) *Labeling.* The Panel is unable to determine suitable labeling. The Panel concludes that no drug labeling claims should be made for vitamin C for the prevention or treatment of the symptoms of the "common cold" until adequate data are available to substantiate such claims. The Panel has discussed such labeling claims above. (See part IX. paragraph B.1.b. above—Vitamins used alone or in combination CCABA products with labeling claims for the prevention or treatment of the "common cold.") The Panel recognizes that vitamin C is readily available as a food supplement to any consumer who so selects to treat the symptoms of the "common cold."

(5) *Evaluation.* Data to demonstrate effectiveness will be required to be completed in 3 years.

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c. *Caffeine.* The Panel concludes that there are insufficient data to permit final classification of caffeine as safe and effective as a "stimulant corrective" for OTC use in combination CCABA products containing central nervous system sedating drugs, such as the antihistamines. The Panel presumes that caffeine has been added as a "stimulant corrective" rather than as an active ingredient. The Panel has discussed this issue earlier in this document. (See part II. paragraph C.5.e. above—Combination products containing correctives (stimulants and sedatives).)

(1) *Safety.* Clinical experience has confirmed that caffeine is generally considered safe in the doses (15 to 30 mg) commonly contained in CCABA combination products.

The Panel is aware of the OTC Sedative, Tranquilizer and Sleep-Aid Drug Product Panel's findings regarding caffeine which were published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292). That Panel concluded that caffeine when used alone and not in a combination drug product is safe and effective for use as a stimulant at a recommended dose of 100 to 200 mg not more often than every 3 to 4 hours.

(2) *Effectiveness.* There are no well-controlled studies demonstrating the effectiveness of caffeine as a "stimulant corrective" in combination CCABA products. The Panel is unaware of any data that support such use in combination products.

(3) *Proposed dosage.* The Panel is unable to determine a proposed dosage. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

(4) *Labeling.* The Panel recommends the labeling claims contained in each drug manufacturer's currently marketed products. In addition, the Panel recommends the activity of caffeine should be identified on the label as "an ingredient added to counteract drowsiness caused by other drugs in this product."

(5) *Evaluation.* Data to demonstrate effectiveness as a stimulant corrective will be required to be completed in 2 years. An acceptable test procedure will be one in which the combination with and without the corrective is evaluated to assess the effectiveness of the corrective to significantly decrease the incidence and/or intensity of the undesirable side effect and the safety of this combination.

d. *Phenobarbital.* The Panel concludes that there are insufficient data to permit final classification of phenobarbital as safe and effective for OTC use as a "stimulant corrective" in combination products with central nervous system stimulant drugs, such as the theophyllines and ephedrine. The Panel presumes that phenobarbital has been added as a "sedative corrective" rather than as a CCABA active ingredient. The Panel has discussed this issue earlier in this document. (See part II. paragraph C.5.e. above—Combination products containing correctives (stimulants and sedatives).)

(1) *Safety.* Clinical experience has confirmed that phenobarbital is generally considered safe in the doses recommended for sedative effect.

The generally recognized dose of phenobarbital as a sedative is 15 to 30 mg given 2 to 4 times daily (Refs. 1 through 3). An official compedium gives a range of 50 to 200 mg daily (Ref. 4). Adverse reactions are infrequent. Effective sedation is usually accompanied by lengthened reaction time (Ref. 5). There are occasional reports of megaloblastic anemia on prolonged use (Ref. 3). Phenobarbital stimulates the synthesis of drug-metabolizing enzymes in the liver, which may increase the metabolism (biotransformation) of other drugs administered at the same time. This type of interaction interferes with obtaining a predictable intensity and/or duration of action of other drugs administered during the period of phenobarbital administration (Refs. 1 through 3). Barbiturates, as a class, are subject to abuse. In patients with acute intermittent porphyria, phenobarbital may precipitate a dangerous rise in the level of porphyrins.

(2) *Effectiveness.* Phenobarbital is used in combination products containing

theophyllines and ephedrine, at a dose of 8 mg, to counteract the central nervous stimulant effect of these drugs. However, the effectiveness of phenobarbital as a "sedative corrective" at a dose of 8 mg has not been established.

The generally recognized dose of phenobarbital as a sedative is 15 to 30 mg given 2 to 4 times daily (Refs. 1 through 3). It would be reasonable to expect that if there is stimulation from other drugs such as ephedrine, the dose to antagonize the stimulation should be at least the minimum effective sedation dose. All the citations in the various volumes submitted state only that a barbiturate is useful in counteracting the stimulant effects of drugs like ephedrine. None suggest a dose. Phenobarbital stimulates hepatic enzymes which may increase the metabolism of other drugs and thereby reduce their expected activity (Refs. 1 and 2). It would seem that the only way to determine the effectiveness of an 8 mg dose of phenobarbital and whether it contributes to the combination of antiasthmatic preparations is by conducting controlled clinical trials.

(3) *Proposed dosage.* Adult oral dosage is 8 to 16 mg every 4 hours.

(4) *Labeling.* The Panel recommends the following: (i) *Indications.* The activity of phenobarbital should be identified on the label as "an ingredient added to counteract nervousness caused by other drugs in this product".

(ii) *Warnings.* (*a*) *"Caution:* May cause drowsiness. Avoid driving a motor vehicle or operating heavy machinery".

(*b*) "Do not take this product if you are presently taking other drugs except under the advice and supervision of a rective":

(*c*) "May be habit-forming".

(5) *Evaluation.* Effectiveness at 8 mg has not been established. Further studies must be completed in 2 years. The Panel recommends the following guidelines to establish effectiveness as a "sedative corrective".

a. *General principles.* Sympathomimetic drugs and theophyllines may cause central nervous system stimulation in some patients. To counteract this a small dose of sedative has been added to some combinations. An experimental protocol should be designed to evaluate the effectiveness of the sedative under the above circumstances and, in addition, it is necessary to show whether the sedative has any additional beneficial or adverse effects on bronchospasm.

b. *Selection of patients.* Testing should be based on the diagnosis of asthma. There should be generalized airway obstruction whose severity varies greatly over a short period of time and this should be demonstrated by pulmonary function tests with significant improvement occurring after the use of a Category I bronchodilator drug.

c. *Methods of study.* The study should consist of testing the bronchodilator drug or drugs without the sedative and in combination with a Category I sedative. The trial should be double-blind and crossover in design. The preparations should probably be given ½ hour before meals to be sure of good absorption. It is suggested that the preparation be given at the manufacturer's suggested dosage 4 times daily for 5 days, and then a crossover alternate be given for a similar period.

Two methods of evaluating the preparation should be involved:

(1) There should be a questionnaire with questions related to nervousness, insomnia, irritability, and tremor. There should also be questions related to the patient's assessment of change in his asthmatic condition. The questionnaire might best be developed in the form of a diary.

(2) Pulmonary function tests and blood gas estimations: The latter are important to determine if the sedative is producing any respiratory depressant effect. These determinations should be done at the beginning of the trial and at the end of the trial before taking the first dose and 1 hour after taking the first dose. Therefore, there should be sets of pulmonary function tests as follows:

(i) First preparation (bronchodilator alone or with a sedative): One half hour before taking the first dose of the first preparation and 1 hour after taking the first dose of the first preparation.

(ii) As above at the end of the 5 days when the last dose of the first preparation is taken.

Evidence of drug effectiveness is required from a minimum of two positive studies based on the results of two different investigators or laboratories.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

(iii) Second preparation (crossover alternate with bronchodilator alone or with a sedative): After an appropriate washout period, the second preparation is given. Determinations are made ½ hour before taking the first dose of the second preparation and 1 hour after taking the first dose of the second preparation.

(iv) As above at the end of the second 5-day series when the last dose of the second preparation is taken.

(v) If possible, repeated estimations of peak expiratory flow rates should be done each day of the 5-day periods, for example, 1 hour after taking the medication.

To obtain sufficient data it will probably be necessary to test about 30 patients.

If the sedative is to be combined with a theophylline it would probably be useful to test for theophylline blood levels at intervals after an oral dose of the theophylline and after an oral dose of the theophylline plus the sedative. This is to determine whether there are any abnormalities of absorption produced. These tests need not be done on asthmatics and could probably be done on volunteers. Probably only 15 individuals need be tested.

From a safety point of view it is assumed that the bronchodilators and sedatives are all in Category I.

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Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)) and the Administrative Procedure Act (secs. 4, 5, 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)) and under authority delegated to him (21 CFR 5.1), (recodification published in the FEDERAL REGISTER of June 15, 1976 (41 FR 24268)) the Commissioner of Food and Drugs proposes that Subchapter D be amended by adding a new Part 341 to read as follows:

PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR AND ANTIASTHMATIC PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Subpart B—Active Ingredients

Subpart C—Testing Procedures

Subpart D—Labeling

AUTHORITY: Secs. 201, 502, 505, 701, 52 Stat. 1040–42 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371); (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—General Provisions

§ 341.1 Scope.

An over-the-counter cold, cough, allergy, bronchodilator or antiasthmatic product in a form suitable for oral, inhalant, or topical administration is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in § 330.1 of this chapter.

§ 341.3 **Definitions.**

As used in this part:

(a) *Age (dosage) range.* Infant or baby (under 2 years), child (2 years to under 12 years), and adult (12 years and over).

(b) *Allergy product.* A drug product used for the relief of the symptoms of allergic rhinitis (such as hay fever).

(c) *Antiasthmatic drug.* A drug product used for the control of the symptoms of bronchial asthma.

(d) *Anticholinergic drug.* A drug used for the relief of excessive secretions of the nose and eyes, symptoms commonly associated with hay fever, allergy, rhinitis, and the "common cold" (cold).

(e) *Antihistaminic drug.* A drug used for the relief of the symptoms of mild allergic rhinitis (such as hay fever) (seasonal allergic rhinitis) and perennial allergic rhinitis.

(f) *Antitussive drug.* A drug which inhibits, controls or suppresses the act of coughing.

(g) *Asthma product.* A drug product used for the control of the symptoms of bronchial asthma.

(h) *Bronchodilator drug.* A drug used to overcome spasms that cause narrowing of the bronchial air tubes, such as in the symptomatic treatment of the wheezing and shortness of breath of asthma.

(i) *Cough product.* A drug product used to inhibit, control or suppress the act of coughing.

(j) *Expectorant drug.* A drug used to promote or facilitate the removal of secretions from the respiratory airways.

(k) *Hay fever product.* A drug product used for the relief of the symptoms of allergic rhinitis (such as hay fever).

(l) *Inhalant dosage.* The dosage range that is generally recognized as safe and effective inhaled nasally or by mouth.

(m) *Nasal decongestant drug.* A drug which reduces nasal congestion caused by acute or chronic rhinitis.

(n) *Oral dosage.* The dosage range that is generally recognized as safe and effective by mouth.

(o) *Topical dosage.* The dosage range that is generally recognized as safe and effective applied topically, such as by external rub for inhalation, as a lozenge for local application by mouth, or as drops or sprays for local application intranasally.

Subpart B—Active Ingredients

§ 341.12 **Antihistamines.**

The active ingredients of the product consist of the following within the dosage limit established for each ingredient:

(a) *Brompheniramine maleate.* Adult oral dosage is 4 mg every 4 to 6 hours not to exceed 24 mg in 24 hours. Children 6 to under 12 years oral dosage is 2 mg every 4 to 6 hours not to exceed 12 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(a). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(b) *Chlorpheniramine maleate.* Adult oral dosage is 4 mg every 4 to 6 hours not to exceed 24 mg in 24 hours. Children 6 to under 12 years oral dosage is 2 mg every 4 to 6 hours not to exceed 12 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(b). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(c) *Diphenhydramine hydrochloride.* Adult oral dosage is 25 to 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 to 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(c). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(d) *Doxylamine succinate.* Adult oral dosage is 7.5 to 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 6 to under 12 years oral dosage is 3.75 to 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(d). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(e) *Methapyrilene preparations.* Adult oral dosage is 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 6 to under 12 years oral dosage is 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(f). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(f) *Phenindamine tartrate.* Adult oral dosage is 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(g). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(g) *Pheniramine maleate.* Adult oral dosage is 12.5 to 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 6.25 to 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(h). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(h) *Promethazine hydrochloride.* Adult oral dosage is 6.25 to 12.5 mg every 8 to 12 hours not to exceed 37.5 mg in 24 hours. Children 6 to under 12 years oral dosage is 3.125 to 6.25 mg every 8 to 12 hours not to exceed 18.75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(i). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(i) *Pyrilamine maleate.* Adult oral dosage is 25 to 50 mg every 6 to 8 hours not to exceed 200 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 to 25 mg every 6 to 8 hours not to exceed 100 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(j). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(j) *Thonzylamine hydrochloride.* Adult oral dosage is 50 to 100 mg every 4 to 6 hours not to exceed 600 mg in 24 hours. Children 6 to 12 years oral dosage is 25 to 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(1). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

§ 341.14 **Antitussives.**

The active ingredients of the product consist of the following within the dosage limit established for each ingredient:

(a) *Codeine preparations (codeine, codeine alkaloid, codeine phosphate, codeine sulfate).* (1) Adult oral dosage is 10 to 20 mg every 4 to 6 hours not to exceed 120 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 to 10 mg every 4 to 6 hours not to exceed 60 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 to 5 mg every 4 to 6 hours not to exceed 30 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(2) Shall apply to products pursuant to the requirements identified in § 329.20(a) and § 1308.15(b) of this chapter.

(b) *Dextromethorphan, dextromethorphan hydrobromide.* Adult oral dosage is 10 to 20 mg every 4 hours or 30 mg every 6 to 8 hours not to exceed 120 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 to 10 mg every 4 hours or 15 mg every 6 to 8 hours not to exceed 60 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 to 5 mg every 4 hours or 7.5 mg every 6 to 8 hours not to exceed 30 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(c) *Diphenhydramine hydrochloride.* Adult oral dosage is 25 mg every 4 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 mg every 4 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(c). For children under 2 years, there is no recomended dosage except under the advice and supervision of a physician.

§ 341.16 **Bronchodilators.**

The active ingredients of the product consist of the following within the dosage limit established for each ingredient:

(a) *Ephedrine preparations, (ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine hydrochloride).* Adult oral dosage is 12.5 to 25 mg not more often than every 4 hours not to exceed 150 mg in 24 hours. Children 2 to under 12 years oral dosage is identified in § 341.90(e). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(b) *Epinephrine preparations (epinephrine, epinephrine bitartrate, epi-*

nephrine hydrochloride (racemic) (inhalant)). Adults and children 4 years and above inhalation dosage is 1 to 3 inhalations of a 1 percent aqueous solution of 1-epinephrine or the equivalent in a pressurized preparation not more often than every 3 hours, except under the advice and supervision of a physician. For children under 4 years, there is no recommended dosage except under the advice and supervision of a physician.

Children and adolescents should not have unsupervised access to this inhaler. There is the possibility of abuse of this material and possible adverse effects on the heart if excessively used.

(c) *Methoxyphenamine hydrochloride.* Adult oral dosage is 100 mg every 4 to 6 hours not to exceed 600 mg in 24 hours. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(d) *Theophylline preparations (aminophylline, theophylline anhydrous, theophylline calcium salicylate, theophylline sodium glycinate).* Adult oral dosage based on the anhydrous theophylline equivalent is 100 to 200 mg every 6 hours not to exceed 800 mg in 24 hours. Children 2 to under 12 years oral dosage is identified in § 341.90(k). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

§ 341.20 Nasal decongestants.

The active ingredients of the product consist of the following within the dosage limit established for each ingredient:

(a) *Ephedrine preparations (ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine hydrochloride) (topical).* Adult topical dosage is 2 to 3 drops or sprays in each nostril of a 0.5 percent aqueous solution not more frequently than every 4 hours. Children 6 to under 12 years topical dosage is 1 or 2 drops or sprays of a 0.5 percent solution not more frequently than every 4 hours. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician.

(b) *Naphazoline hydrochloride (topical).* Adult topical dosage is 1 to 2 drops or sprays of a 0.05 percent aqueous solution in each nostril not more frequently than every 6 hours. Children 6 to under 12 years topical dosage is 1 to 2 drops or sprays of a 0.025 percent aqueous solution in each nostril not more frequently than every 6 hours. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician.

(c) *Oxymetazoline hydrochloride (topical).* Adults and children 6 to under 12 years topical dosage is 2 to 3 drops or sprays of a 0.05 percent aqueous solution in each nostril 2 times daily (in the morning and evening). Children 2 to under 6 years topical dosage is 2 to 3 drops of a 0.025 percent aqueous solution in each nostril 2 times daily (in the morning and evening). Only drops should be used in children 2 to under 6 years since the spray is difficult to use in the small nostril. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(d) *Phenylephrine hydrochloride (oral/topical*—(1) *As an oral nasal decongestant.* Adult oral dosage is 10 mg every 4 hours not to exceed 60 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 mg every 4 hours not to exceed 30 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 mg every 4 hours not to exceed 15 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(2) *As a topical nasal decongestant.* Adult topical dosage is 2 to 3 drops or sprays in each nostril of a 0.25 to 0.5 percent aqueous solution not more frequently than every 4 hours. Children 6 to under 12 years topical dosage is 2 to 3 drops or sprays in each nostril of a 0.25 percent aqueous solution not more frequently than every 4 hours. Children 2 to under 6 years topical dosage is 2 to 3 drops in each nostril of a 0.125 percent aqueous solution not more frequently than every 4 hours. Only drops should be used in children 2 to under 6 years since the spray is difficult to use in the small nostril. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(e) *Phenylpropanolamine preparations (phenylpropanolamine bitartrate, phenylpropanolamine hydrochloride, phenylpropanolamine maleate) (oral).* Dosages are based on the phenylpropanolamine hydrochloride equivalent. Adult oral dosage is 25 mg every 4 hours or 50 mg every 8 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 mg every 4 hours or 25 mg every 8 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is 6.25 mg every 4 hours or 12.5 mg every 8 hours not to exceed 37.5 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(f) *Propylhexedrine (inhalant).* Adults and children 6 to under 12 years inhalant dosage from an inhaler that shall deliver in each 800 ml of air 0.40 to 0.50 mg of propylhexedrine is 2 inhalations in each nostril not more frequently than every 2 hours. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician. The inhaler should retain effectiveness for a minimum of 2 to 3 months.

(g) *Pseudoephedrine preparations (pseudoephedrine hydrochloride, pseudoephedrine sulfate) (oral).* Adult oral dosage is 60 mg every 4 hours not to exceed a maximum of 360 mg in 24 hours. Children 6 to under 12 years oral dosage is 30 mg every 4 hours not to exceed 180 mg in 24 hours. Children 2 to under 6 years oral dosage is 15 mg every 4 hours not to exceed 90 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(h) *Xylometazoline hydrochloride (topical).* Adult topical dosage is 2 to 3 drops or sprays in each nostril of a 0.1 percent aqueous solution every 8 to 10 hours. Children 2 to under 12 years topical dosage is 2 to 3 drops or sprays in each nostril of a 0.05 percent aqueous solution every 8 to 10 hours. Only drops should be used in children 2 to under 6 years since the spray is difficult to use in the small nostril. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

§ 341.40 Permitted combinations of active ingredients.

(a) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single generally recognized as safe and effective analgesic-antipyretic active ingredient: *Provided,* That the combination contains any applicable labeling identified in § 341.85(d).

(b) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20.

(c) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20 with any single generally recognized as safe and effective analgesic-antipyretic active ingredient: *Provided,* That the combination contains the labeling identified in § 341.85(d).

(d) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single antitussive active ingredient identified in § 341.14: *Provided,* That the combination contains the labeling identified in § 341.85(a).

(e) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20 with any single antitussive active ingredient identified in § 341.14.

(f) Any single antitussive active ingredient identified in § 341.14 may be combined with any single oral bronchodilator active ingredient identified in § 341.16: *Provided,* That the combination contains the labeling identified in § 341.85(b).

(g) Any single antitussive active ingredient identified in § 341.14 may be combined with any single generally recognized as safe and effective expectorant active ingredient.

(h) Any single antitussive active ingredient identified in § 341.14 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20.

(i) Any single antitussive active ingredient identified in § 413.14 may be combined with any single generally recognized as safe and effective expectorant active ingredient with any single oral nasal decongestant active ingredient identified in § 341.20.

(j) Any single antitussive active ingredient identified in § 341.14 may be combined with any single generally recognized as safe and effective local anesthetic or local analgesic active in-

gredient: *Provided,* That the product is available only as a lozenge.

(k) Any single bronchodilator active ingredient identified in § 341.16(a) may be combined with any single bronchodilator active ingredient identified in § 341.16(d).

(l) Any single oral bronchodilator active ingredient identified in § 341.16 may be combined with any single generally recognized as safe and effective expectorant active ingredient: *Provided,* That the combination contains the labeling identified in § 341.85(c).

(m) Any single oral nasal decongestant active ingredient identified in § 341.20 may be combined with any single generally recognized as safe and effective analgesic-antipyretic active ingredient: *Provided,* That the combination contains the labeling identified in § 341.85(d).

(n) Any single oral nasal decongestant active ingredient identified in § 341.20 may be combined with any single generally recognized as safe and effective expectorant active ingredient.

(o) Any single nasal decongestant active ingredient identified in § 341.20 may be combined with any single generally recognized as safe and effective local anesthetic or local analgesic active ingredient: *Provided,* That the product is available only as a lozenge.

Subpart C—Testing Procedures

§ 341.45 Theophylline tablet dissolution testing.

All tablet product formulations containing theophylline preparation(s) identified in § 341.16(d) shall be tested according to the procedures described in the United States Pharmacopeia XIX (page 651). The tablets shall be suitable for OTC use if the quantity of theophylline dissolved within 15 minutes is not less than 50 percent of the labeled amount, based on the anhydrous theophylline, equivalent content, and the quantity of theoplylline dissolved within 30 minutes is not less than 90 percent of the labeled amount of theophylline, based on the anhydrous theophylline equivalent content, for each of the tablets tested. The resulting data shall be submitted by petition to the Food and Drug Administration for approval prior to use. The petition and the data contained therein shall be maintained in a permanent file for public review by the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852.

Subpart D—Labeling

§ 341.50 Labeling of cold, cough, allergy, bronchodilator, and antiasthmatic products.

(a) *Indications.* (1) The labeling shall identify the product pursuant to the appropriate definition(s) established in § 341.3 and shall contain the applicable labeling for the active ingredient(s) as set forth in §§ 341.70, 341.72, 341.74, 341.76, 341.78, and 341.80.

(2) In addition, labeling may also contain the following indication(s): *Provided,* That such phrase(s) is combined and contiguous with the indications required as set forth in § 341.50(a)(i):

(i) "as may be associated with the common cold (cold)."

(ii) "as may occur in the common cold (cold)."

(b) *Directions for use.* The labeling of the product contains the recommended dosage and appropriate directions identified under §§ 341.12, 341.14, 341.16, or 341.20 under the heading "Directions," per time interval, e.g., every 4 hours, or other time period, e.g., 3 times daily, broken down by age groups, if appropriate, followed by "or as directed by a physician."

(c) *Warnings.* The labeling of the product contains the appropriate warning(s) under §§ 341.70, 341.72, 341.74, 341.76, 341.78, or 341.80 and, if applicable, the following general warning under the heading "Warning," which may be combined to eliminate duplicative words or phrases so the resulting warning is clear and understandable. For products containing an alcoholic content greater than 10 percent (weight/weight) "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(d) *Drug interaction precautions.* The labeling of the product, where appropriate under § 341.76 or § 341.80, contains drug interaction precautions, under the heading "Drug Interaction Precautions".

§ 341.70 Products containing anticholinergics.

(a) *Indications.* The labeling of the product shall contain any of the following indications, under the heading "Indications":

(1) "For temporary relief of watery nasal discharge and watering eyes as may occur in certain allergic conditions and infections of the upper respiratory tract".

(2) "Temporarily suppresses watery nasal discharge".

(3) "Temporary relief from excessive nasal secretions".

(4) "Temporary relief from running nose".

(5) "Temporarily suppresses watering of eyes".

(b) *Warnings.* The labeling of the product contains the following warnings, under the heading "Warning":

(1) "Do not exceed recommended dosage except under the advice and supervision of a physician".

(2) "Do not continue to take this product if constipation, excessive dryness of the mouth, insomnia, excitement, confusion, rapid pulse, or blurring of vision occur".

(3) *"Caution:* Do not take this product if you have asthma, glaucoma or have difficulty in urination due to enlargement of the prostate gland except under the advice and supervision of a physician".

(4) "Do not give this product to children under 12 years except under the advice and supervision of a physician".

§ 341.72 Products containing antihistamines.

(a) *Indications.* The labeling of the product shall contain any of the following indications, under the heading "Indications":

(1) "Alleviates, decreases, or for temporary relief of, running nose, sneezing, itching of the nose or throat and itchy and watery eyes as may occur in allergic rhinitis (such as hay fever)".

(2) "Alleviates, decreases, or for temporary relief of, running nose as may occur in allergic rhinitis (such as hay fever)".

(3) "Alleviates, decreases, or for temporary relief of, sneezing as may occur in allergic rhinitis (such as hay fever)".

(4) "Alleviates, decreases, or for temporary relief of, itching of the nose or throat as may occur in allergic rhinitis (such as hay fever)".

(5) "Alleviates, decreases, or for temporary relief of, itchy and watery eyes as may occur in allergic rhinitis (such as hay fever)".

(6) "Dries running nose as may occur in allergic rhinitis (such as hay fever)".

(b) *Warnings.* The labeling of the product contains the following warnings, under the heading "Warnings":

(1) "May cause excitability especially in children".

(2) "Do not take this product if you have asthma, glaucoma or difficulty in urination due to enlargement of the prostrate gland except under the advice and supervision of a physician".

(3) *"Caution:* Avoid driving a motor vehicle or operating heavy machinery".

(4) *"Caution:* Avoid alcoholic beverages while taking this product".

(5) "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(6) For products containing the active ingredients identified in paragraphs (a), (b), (f), (i), and (j) of § 341.12: "May cause drowsiness".

(7) For products containing the active ingredients identified in paragraphs (c), (d), (e), (g), and (h) of § 341.12: "May cause marked drowsiness".

(8) For products containing an active ingredient identified in § 341.12(f): *"Caution:* May cause nervousness and insomnia in some individuals".

§ 341.74 Products containing antitussives.

(a) *Indications.* The labeling of the product may contain any of the following indications, under the heading "Indications": (1) "Cough suppressant which temporarily reduces the impulse to cough".

(2) "For the temporary relief of cough due to minor throat and bronchial irritation as may occur with the common cold (cold) or with inhaled irritants".

(3) "Temporarily quiets coughing by its antitussive action".

(4) "Temporarily helps you cough less".

(5) "Temporarily helps to quiet the cough reflex that causes coughing".

(6) For products containing an ingredient identified in § 341.14(a): "Calms the cough control center and relieves coughing".

(7) For products containing an ingredient identified in § 341.14 (b) and (c):

(i) "Calms the cough control center and relieves coughing".

(ii) "Non-narcotic cough suppressant for the temporary control of coughs".

(iii) "Calms cough impulses without narcotics".

(b) *Warnings.* The labeling of the product contains the following warnings, under the heading "Warnings": (1) "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(2) "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a physician".

(3) *"Caution:* A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur or is accompanied by high fever, rash or persistent headache, consult a physician".

(4) For products containing an ingredient identified in § 341.14(a):

(i) "May cause or aggravate constipation".

(ii) "Do not give this product to children taking other drugs except under the advice and supervision of a physician".

(iii) "Do not take this product if you have a chronic pulmonary disease or shortness of breath except under the advice and supervision of a physician".

(5) For products containing an ingredient identified in § 341.14(c): (i) May cause marked drowsiness".

(ii) "May cause excitability especially in children".

(iii) "Do not take this product if you have glaucoma or have difficulty in urination due to enlargement of the prostate gland except under the advice and supervision of a physician".

(iv) "Caution: Avoid driving a motor vehicle or operating heavy machinery".

(v) "Do not give this product to children under 6 years except under the advice and supervision of a physician".

§ 341.76 Products containing bronchodilators.

(a) *Indications.* (1) The labeling of a product to be taken by inhalation may contain under the heading "Indications" the time to onset of action expressed in minutes.

(2) The labeling of the product shall contain any of the following indications, under the heading "Indications":

(i) "For temporary relief of bronchial asthma".

(ii) "For symptomatic control of bronchial asthma".

(iii) "Provides temporary relief from acute symptoms of bronchial asthma".

(iv) "Relaxes tense bronchial muscles to ease breathing for asthma patients".

(v) "For temporary relief of wheezing (attacks and distress) of bronchial asthma".

(b) *Warnings.* The labeling of the product contains the following warning, under the heading "Warnings": (1) "Caution: Do not take this product unless a diagnosis of asthma has been made by a physician".

(2) For products containing an ingredient identified in § 341.16 (a) and (c):

(i) *"Caution:* Do not continue to take this product but seek medical assistance immediately if symptoms are not relieved within 1 hour or become worse".

(ii) "Nervousness, tremor, sleeplessness, nausea and loss of appetite may occur".

(iii) "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes or difficulty in urination due to enlargement of the prostate gland".

(iv) *Drug interaction precaution.* "Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor".

(v) "Do not give this product to children under 12 years except under the advice and supervision of a physician".

(3) For products containing an ingredient identified in § 341.16(b):

(i) "Do not take this product at higher than recommended doses except under the advice and supervision of a physician for it may cause nervousness and rapid heart beat".

(ii) *"Caution:* Do not continue to take this product but seek medical assistance immediately if symptoms are not relieved within 20 minutes or become worse".

(iii) "Do not take this product if you have heart disease or high blood pressure except under the advice and supervision of a physician".

(iv) *Drug interaction precaution.* "Do not take this product of you are presently taking a prescription antihypertensive or antidepressant drug containing a monamine oxidase inhibitor".

(v) "Keep this product out of reach of children and adolescents because unsupervised access may cause abuse or possible adverse effects on the heart if excessively used".

(vi) "Do not give this product to children under 4 years except under the advice and supervision of a physician".

(4) For products containing an ingredient identified in § 341.16(d):

(i) "Do not exceed recommended dosage except under the advice and supervision of a physician".

(ii) "Do not take this product if nausea, vomiting or restlessness occurs".

(iii) *"Caution:* Do not continue to take this product but seek medical assistance immediately if symptoms are not relieved within 1 hour or become worse".

(iv) "Do not take this product if you are presently taking a drug or suppository containing any form of theophylline except under the advice and supervision of a physician".

(v) "Do not give this product to children under 12 years except under the advice and supervision of a physician. Excessive use may cause toxic effects and even death in children".

§ 341.78 Products containing expectorants.

(a) *Indication.* The labeling of the product may contain any of the following indications, under the heading "Indications":

(1) "Helps loosen phlegm (sputum)".

(2) "Helps rid the passageways of bothersome mucus".

(3) "Expectorant action to help loosen phlegm (sputum) and bronchial secretions".

(4) "Helps drainage of bronchial tubes by thinning the mucus".

(5) "Relieves irritated membranes in the respiratory passageways by preventing dryness through increased mucus flow".

(b) *Warnings.* The labeling of the product contains the following warnings, under the heading, "Warnings":

(1) "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(2) "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a physician".

(3) *"Caution:* A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur or is accompanied by high fever, rash or persistent headache, consult a physician".

§ 341.80 Products containing nasal decongestants.

(a) *Indications.* The labeling of the product shall contain any of the following indications, under the heading "Indications":

(1) "For temporary relief of nasal congestion due to the common cold (cold)".

(2) "For temporary relief of nasal congestion due to hay fever or other upper respiratory allergies".

(3) "For temporary relief of nasal congestion associated with sinusitus".

(4) "For the temporary relief of stuffy nose (stopped up nose, nasal stuffiness, clogged up nose)".

(5) "Reduces swelling of nasal passages; shrinks swollen membranes".

(6) "Decongest nasal passages".

(7) "Temporarily restores freer breathing through the nose".

(8) "Helps clear nasal passages".

(9) "Helps decongest sinus openings, sinus passages".

(10) "Promotes nasal and/or sinus drainage".

(11) For products with claims for duration of effect: Statements as to duration of effect must be substantiated and accompanied by a specific time period expressed in minutes or hours, as appropriate.

(12) For products to be used as topical nasal decongestants with claims for rapid onset of action: Statements relating to time to onset of action, such as, "fast" or "quick", must be accompanied by a specific time period expressed in minutes.

(13) For products to be used as topical nasal decongestants which can demonstrate a cooling sensation:

(i) "Provides cooling sensation".

(ii) "Cooling".

(iii) "Cools nasal passages".

(b) *Warnings.* The label of the product contains the following warnings, under the heading "Warnings".

(1) For products containing topical nasal decongestants:

(i) "Do not exceed recommended dosage because symptoms may occur such as burning, stinging, sneezing, or increase of nasal discharge.

(ii) "Do not use this product for more than 3 days. If symptoms persist, consult a physician".

(iii) "The use of this dispenser by more than one person may spread infection".

(2) For products used as oral nasal decongestants:

(i) "Do not exceed recommended dosage because at higher doses nervousness, dizziness, or sleeplessness may occur".

(ii) "If symptoms do not improve within 7 days or are accompanied by high fever, consult a physician before continuing use".

(iii) "Do not take this preparation if you have high blood pressure, heart disease, diabetes, or thyroid disease except under the advice and supervision of a physician".

(iv) *"Drug interaction precaution:* Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor except under the advice and supervision of a physician".

(3) For products used as inhalant nasal decongestants:

(i) "This inhaler should be warmed in the hand before use to increase effectiveness".

(ii) "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(iii) "Children should not have unsupervised access to this inhaler".

(iv) *"Caution:* Not for use by mouth".

(4) For products containing the active ingredient identified in § 341.20(a) at a concentration of 0.5 percent: "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(5) For products containing the active ingredient identified in § 341.20(b) at a concentration of 0.025 percent: "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(6) For products containing the active ingredient identified in § 341.20(b) at a concentration of 0.05 percent: "For adult use only. Do not give this product to children under 6 years since it may cause sedation if swallowed".

(7) For products containing the active ingredient identified in § 341.20(d) (2) at a concentration of 0.125 percent: "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(8) For products containing the active ingredient identified in § 341.20(d) (2) at a concentration of 0.25 percent: "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(9) For products containing the active ingredient identified in § 341.20(d) (2) at a concentration of 0.5 percent: "For adult use only. Do not give this product to children under 12 years except under the advice and supervision of a physician".

(10) For products containing the active ingredient identified in § 341.20(h) at a concentration of 0.05 percent: "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(11) For products containing the active ingredient identified in § 341.20(h) at a concentration of 0.1 percent: "For adult use only. Do not give this product to children under 12 years except under the advice and supervision of a physician".

§ 341.85 Labeling of combinations of active ingredients.

(a) *Antihistamine combined with an antitussive.* A combination identified in § 341.40(d) shall contain the following warning under the heading "Warning": "Caution: May cause marked drowsiness". The Food and Drug Administration will grant an exemption to the labeling term "marked", which may be removed from the warning statement upon petition if adequate data are submitted to demonstrate that the combination product does not cause a significant increase in drowsiness as compared with each active ingredient when tested alone. The petition and the data contained therein shall be maintained in a permanent file for public review by the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852.

(b) *Antitussive combined with a bronchodilator.* A combination identified in § 341.40(f) shall contain the following warning, under the heading "Warning": "This product should be used only for cough associated with asthma".

(c) *Bronchodilator combined with an expectorant.* A combination identified in § 341.40(1) shall contain the following warning, under the heading "Warning": "This product should be used only for cough associated with asthma".

(d) *Aspirin (acetylsalicylic acid) containing combinations.* Any combination identified in § 341.40 (a), (c), or (m) containing aspirin (acetylsalicylic acid) shall contain the following warning, under the heading "Warning": "This product contains aspirin and should not be taken by individuals who are sensitive to aspirin".

§ 341.90 Professional labeling.

The labeling of the product provided to health professionals (but not to the general public) may contain the following additional dosage information for products containing the active ingredients identified below:

(a) For products containing brompheniramine maleate: Children 2 to under 6 years oral dosage is 1 mg every 4 to 6 hours not to exceed 6 mg in 24 hours.

(b) For products containing chlorpheniramine maleate: Children 2 to under 6 years oral dosage is 1 mg every 4 to 6 hours not to exceed 6 mg in 24 hours.

(c) For products containing diphenhydramine hydrochloride:

(1) *For use as an antihistamine:* Children 2 to under 6 years oral dosage is 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours.

(2) *For use as an antitussive:* Children 2 to under 6 years oral dosage is 6.25 mg every 4 hours not to exceed 37.5 mg in 24 hours.

(d) *For products containing doxylamine succinate:* Children 2 to under 6 years oral dosage is 1.9 to 3.125 mg every 4 to 6 hours not to exceed 18.75 mg in 24 hours.

(e) *For products containing ephedrine preparations for use as a bronchodilator (ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine hydrochloride):* Children 6 to under 12 years oral dosage is 6.25 to 12.5 mg not more often than every 4 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is 0.3 to 0.5 mg/kg of body weight not more often than every 4 hours not to exceed 2 mg/kg of body weight in 24 hours.

(f) *For products containing methapyrilene preparations (methapyrilene fumarate, methapyrilene hydrochloride):* Children 2 to under 6 years oral dosage is 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours.

(g) *For products containing pheninda-mine tartrate:* Children 2 to under 6 years oral dosage is 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours.

(h) *For products containing phenira-mine maleate:* Children 2 to under 6 years oral dosage is 3.125 to 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours.

(i) *For products containing promethazine hydrochloride:* Children 2 to under 6 years oral dosage is 1.56 to 3.125 mg every 8 to 12 hours not to exceed 9.375 mg in 24 hours.

(j) *For products containing pyrilamine maleate:* Children 2 to under 6 years oral dosage is 6.25 to 12.5 mg every 6 to 8 hours not to exceed 50 mg in 24 hours.

(k) *For products containing theophylline preparations (aminophylline, theophylline anhydrous, theophylline calcium salicylate, theophylline sodium glycinate):* Children 2 to under 12 years oral dosage based on the anhydrous theophylline equivalent is 3.33 mg/kg of body weight 3 times daily every 8 hours not to exceed 10 mg/kg in 24 hours.

(l) For products containing thonzylamine hydrochloride: Children 2 to under 6 years oral dosage is 12.5 to 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours.

Interested persons are invited to submit their comments in writing (preferably in quintuplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal on or before December 8, 1976. Such comments should be addressed to the office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852, and may be accompanied by a memorandum or brief in support thereof. Additional comments replying to any comments so filed may also be submitted on or before January 7, 1977. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: July 30, 1976.

SHERWIN GARDNER,
Acting Commissioner of Food and Drugs.

[FR Doc.76–22710 Filed 9–8–76;8:45 am]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 76N-052N]

21 CFR Part 341

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for Over-the-Counter Nasal Decongestant Drug Products

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) nasal decongestant drug products (drug products used for relieving the symptom of nasal congestion caused by acute or chronic rhinitis) are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. This proposal deals only with nasal decongestant drug products and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs on the proposed regulation by May 15, 1985. New data by January 15, 1986. Comments on the new data by March 17, 1986. These dates are consistent with the time periods specified in the agency's revised procedural regulations for reviewing and classifying OTC drugs (21 CFR 330.10). Written comments on the agency's economic impact determination by May 15, 1985.

ADDRESS: Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drugs and Biologics (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of September 9, 1976 (41 FR 38312), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products, together with the recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthamatic Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in these drug classes. Interested persons were invited to submit comments by December 8, 1976. Reply comments in response to comments filed in the initial comment period could be submitted by January 7, 1977.

In a notice published in the **Federal Register** of March 21, 1980 (45 FR 18400), the agency advised that it had reopened the administrative record for OTC cold, cough, allergy, bronchodilator, and antiasthamatic drug products to allow for consideration of data and information that had been filed in the Dockets Management Branch after the date the administrative record previously had officially closed. The agency concluded that any new data and information filed prior to March 21, 1980 should be available to the agency in developing a proposed regulation in the form of a tentative final monograph.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information. Data and information received after the administrative record was reopened have also been put on display in the Dockets Management Branch. In response to the advance notice of proposed rulemaking, 16 manufacturers, 2 manufacturers' associations, 4 consumers, the staff members of one bureau of a government agency, 19 health care professionals, and 5 health care professional societies submitted comments on nasal decongestants. One manufacturer submitted a reply comment. Copies of the comments received are on public display in the Dockets Management Branch.

FDA is issuing the tentative final monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products in segments. This document on nasal decongestant drug products is the fourth segment to be published. The first segment, on anticholinergic drug products and expectorant drug products, was published in the **Federal Register** of July 9, 1982 (47 FR 30002). The second segment, on bronchodilator drug products, was published in the **Federal Register** of October 26, 1982 (47 FR 47520). The third segment, on antitussive drug products, was published in the **Federal Register** of October 19, 1983; 48 FR 48576). The fifth segment, on antihistamine drug products, is being published elsewhere in this issue of the **Federal Register**. A subsequent segment on combination drug products and general comments will be published in a future issue of the **Federal Register**.

The advance notice of proposed rulemaking, which was published in the **Federal Register** on September 9, 1976 (41 FR 38312), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the present document is designated in the OTC drug review regulations as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule) the FDA states for the first time its position on the establishment of a monograph for OTC nasal decongestant drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC nasal decongestant drug products.

This tentative final monograph would amend Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations in Part 341 (as set forth in the tentative final monograph on anticholinergic drug products and expectorant drug products that was published in the **Federal Register** of July 9, 1982 (47 FR 30002)) in Subpart A, by adding in § 341.3, new paragraphs (h) and (i); in Subpart B, by adding new § 341.20; and in Subpart C, by adding new § 341.80, and by adding in § 341.90, new paragraphs (m) and (n). This proposal constitutes FDA's tentative adoption of the Panel's conclusion and recommendations on OTC nasal decongestant drug products, as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them.

The OTC procedural regulations (21 CFR 330.10) have been revised to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). (See the **Federal Register** of September

29, 1981; 46 FR 47730.) The Court in *Cutler* held that the OTC drug review regulations were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision has been deleted from the regulations, which now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process, before the establishment of a final monograph.

Although it was not required to do so under *Cutler*, FDA will no longer use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but will use instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the **Federal Register**. On or after that date, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced into interstate commerce unless they are the subject of an approved new drug application (NDA). Further, any OTC drug products subject to this monograph that are repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In the advance notice of proposed rulemaking for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products (published in the **Federal Register** of September 9, 1976 (41 FR 38312)), the agency suggested that the conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the **Federal Register** and that the conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of whether further testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products will have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and if further reformulation is required, there could be a further delay in having a new product available for manufacture.

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss, but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the **Federal Register**. The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and have their products in compliance in the marketplace. However, if the agency determines that any labeling for a condition included in the final monograph should be implemented sooner, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notice published in the **Federal Register** of August 9, 1972 (37 FR 16029) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

The Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products recommended that phenylpropanolamine preparations be classified in Category I for nasal decongestant use at adult oral dosages equivalent to these phenylpropanolamine hydrochloride dosages: 25 milligrams (mg) every 4 hours or 50 mg every 6 hours not to exceed 150 mg in 24 hours (see 41 FR 38420; September 9, 1976). Similarly, the Advisory Review Panel on OTC Miscellaneous Internal Drug Products recommended that phenylpropanolamine hydrochloride be classified as Category I for appetite control use in adult oral dosages of 25 to 50 mg, not exceeding 150 mg daily. (See 47 FR 8484; February 26, 1982.) However, FDA became aware of reports of studies, made available after the Panels' reports had been submitted, indicating that certain dosages of phenylpropanolamine cause blood pressure elevation. These studies were discussed in the preamble to the advance notice of proposed rulemaking for OTC weight control drug products (47 FR 8466–8468). At that time, the agency specifically requested comments and information on the extent to which phenylpropanolamine induces or aggravates hypertension and interacts with medications that inhibit prostaglandin synthesis.

Numerous comments on the recommended phenylpropanolamine dosage levels and related issues have been submitted to FDA in both the OTC weight control and the OTC nasal decongestant rulemakings. Because the issues concerning the safety of phenylpropanolamine for weight control use and for nasal decongestant use are closely related, the agency has decided to address these issues in the **Federal Register** publication to be published in the near future. Therefore, phenylpropanolamine preparations will not be categorized or further discussed in this tentative final monograph for OTC nasal decongestant drug products.

I. The Agency's Tentative Conclusions on the Comments

A. General Comments on Nasal Decongestant Drug Products

1. One comment stated that there is no evidence that "so-called nasal

decongestants" are of any clinical value. No data or published references were submitted or cited to support this statement.

The Panel reviewed the scientific literature and data submissions, listened to testimony from interested parties, and considered all other available data and information before categorizing OTC nasal decongestant active ingredients. The Panel classified in Category I those active ingredients for which it had appropriate supportive data to establish general recognition of safety and effectiveness. In addition, the Panel placed in Category III those active ingredients for which it did not have sufficient data to establish safety and effectiveness. Additional data must be submitted on these Category III ingredients before they can be generally recognized as safe and effective. The agency believes that those ingredients which have been categorized as safe and effective do have clinical value for the indications listed in this tentative final monograph.

2. One comment disagreed with the Panel's recommendation that claims such as "most recommended by doctors" be placed in Category II because such claims are difficult to substantiate. The comment contended that "difficulty in substantiating does not imply inability to substantiate." Thus, according to the comment, the Panel's reasoning justifies placing this type of claim in Category III. More importantly, the comment argued, this type of claim is not specifically related to safety or effectiveness. If this type of statement were true, the comment contended, banning its use is an inappropriate prior restraint and in violation of the First Amendment to the Constitution.

The OTC drug review program establishes conditions under which OTC drugs are generally recognized as safe and effective and not misbranded. Two principal conditions examined during the review are allowable ingredients and allowable labeling. The FDA has determined that it is not practical—in terms of time, resources, and other considerations—to set standards for all labeling found in OTC drug products. Accordingly, OTC drug monographs regulate only labeling related in a significant way to the safe and effective use of covered products by lay persons. OTC drug monographs establish allowable labeling for the following items: product statement of identity; names of active ingredients; indications for use; directions for use; warnings against unsafe use, side effects, and adverse reactions; and claims concerning mechanism of drug action.

The agency believes terms such as "most recommended by doctors" are unrelated to the characteristics of the drugs in question and, therefore, do not relate in a significant way to the drugs' safe and effective use. Accordingly, the term "most recommended by doctors" is outside the scope of the OTC drug review. The agency emphasizes that even though terms such as "most recommended by doctors" are outside the scope of the OTC drug review, they are subject to the prohibitions in section 502 of the act (21 U.S.C. 352) relating to labeling that is false of misleading. Such statements or terms will be evaluated by the agency on a product-by-product basis, under the provisions of section 502 of the act (21 U.S.C. 352) relating to labeling that is false or misleading.

Moreover, any statement or term that is outside the scope of the monograph, even though it is truthful and not misleading, may not appear in any portion of the labeling required by the monograph and may not detract from such required information. However, statements and terms outside the scope of the monograph may be included elsewhere in the labeling, provided they are not false or misleading.

3. One comment stated that two nasal decongestants should not be taken simultaneously and recommended that the labeling should be clear on this matter. The comment did not further elaborate on its statement.

The agency believes that the comment is referring to two different drug products, each containing a nasal decongestant, for similar uses. The proposed labeling for nasal decongestants in this tentative final monograph specifically requires that the product's principal intended use, i.e., "nasal decongestant" be stated in the labeling. Further, all products containing a nasal decongestant will bear similar indications for use. By reading the label, the consumer should understand that two different drug products containing nasal decongestants are intended to treat the same symptoms and should not be taken simultaneously. The agency, therefore, believes that two nasal decongestants contained in different products will not inadvertently be taken simultaneously because the proposed labeling for nasal decongestants is explicit enough to inform the consumer of the proper use of these drugs. In addition, the agency is unaware of any data that indicate that the proposed labeling for nasal decongestants is inadequate to prevent the inadvertent use of two nasal decongestants simultaneously. (Note: the combination of two nasal decongestants in the same product will be discussed in the combinations segment of the tentative final monograph in a future issue of the **Federal Register**.)

B. Comments on the Switch of Prescription Nasal Decongestants to OTC Status

4. Several comments agreed with the Panel's classification of oxymetazoline hydrochloride and xylometazoline hydrochloride as Category I OTC topical nasal decongestants. Other comments were opposed to the OTC availability of these ingredients for various reasons. Several comments stated that the habituation and rebound congestion caused by these drugs contraindicated their OTC availability. One comment petitioned the FDA to remove oxymetazoline hydrochloride nasal spray and nasal solution from the OTC market because it is a new drug and the subject of a new drug application which limits its introduction into interstate commerce as a prescription only product. Another comment stated that the use of a xylometazoline hydrochloride nasal spray was the probable cause of a specific incident of severe cardiac upset.

The agency's position regarding the marketing status of ingredients recommended for OTC use which had previously been limited to prescription use is contained in the Code of Federal Regulations at 21 CFR 330.13(b)(2). This regulation explains that such ingredients placed in Category I by a Panel may be marketed OTC following publication of the Panel's proposed monograph subject to the risk that the Commissioner may not accept the Panel's recommendation and may instead adopt a different position that may require relabeling, recall, or other regulatory action. Because the Panel considered oxymetazoline hydrochloride safe, it recommended that this drug, previously available only by prescription prior to publication of the Panel's report in the **Federal Register**, be reclassified to permit OTC use. Because oxymetazoline has been placed in Category I and the Panel's report has been published without an agency dissent, a manufacturer may market the drug OTC, prior to promulgation of a final monograph, subject to the risk that the Commissioner may subsequently adopt a position different from the Panel's recommendation.

The agency recognizes the problem of rebound congestion associated with the use of topical nasal decongestants. Rebound congestion occurs when

topical nasal decongestants are used too frequently and for too long a period of time. The nasal mucous membranes become more congested and edematous as the drug's vasoconstrictor effect subsides. This effect leads to continued use of the drug and perpetuation of the rebound phenomenon. The Panel also addressed this problem and recommended that all nasal drops and sprays be labeled to limit use to not more than 3 days so as to discourage prolonged use. The Panel also recommended labeling that advised the consumer to consult a doctor if symptoms persisted after 3 days of use. (See § 341.80(b)(1)(ii), 41 FR 38423.) Although aware that continued use of these drugs might result in rebound congestion, the Panel thought that the clinical and marketing data it reviewed showed these drugs to be safe and effective when used according to label directions. Therefore, the Panel concluded that the drug should be available for OTC use.

From the information available, the agency cannot determine the cause of the cardiac upset reported in one of the comments. However, it is reported in the literature that the imidazolines (a class of drugs which includes naphazoline hydrochloride, oxymetazoline hydrochloride, and xylometazoline hydrochloride) may cause arrhythmias, presumably due to coronary vasoconstriction (Ref. 1). Because of these effects, the imidazolines should be used sparingly and with caution in infants, young children, and patients with cardiovascular disease (Refs. 1 and 2).

Studies of the effect of the imidazolines on the intestinal smooth muscle of the rabbit and on the cardiovascular system of the cat showed that the pharmacological action of these drugs, particularly oxymetazoline, is strong (Ref. 3). Nasal decongestants that are administered orally are known to be capable of producing systemic effects. Consequently, the Panel recommended a warning to persons with high blood pressure, heart disease, diabetes, or thyroid disease not to take the drug except under the advice and supervision of a physican. (See § 341.80(b)(2)(iii), 41 FR 38423.) A warning that the product should be used very cautiously in patients with hyperthyroidism, coronary artery disease, hypertension, and diabetes mellitus has also been required for prescription topical nasal decongestants containing oxymetazoline and xylometazoline for over 10 years (Refs. 4 and 5). Because the Panel believed that absorption of the drug into the general circulation was negligible following topical use, the Panel did not recommend a similar warning statement; therefore, the above warning was not required for these products marketed on an OTC basis pursuant to § 330.13 following publication of the Panel's report.

The agency believes that use of these drugs in a generally healthy person is safe, but is concerned that systemic effects can occur in small children or in persons with cardiovascular disease as a result of absorption from the gastrointestinal tract if an excessive amount of the drug is swallowed. Because some of the drug is often swallowed when nose drops and sprays are administered, systemic effects such as those occurring from an orally administered dose can occur. Because of the possibility of generalized vasoconstriction and tachycardia, persons with hypertension, heart disease, diabetes, or hyperthyroidism should only use nasal decongestants as directed by a doctor (Refs. 1, 2, 4, 5, and 6).

Use of these drugs can also produce effects which could alter the balance of insulin and glucose in a diabetic patient (Refs. 6 and 7). Additionally, because of the vascular problems which frequently accompany diabetes, diabetic patients should consult a doctor before using topical nasal decongestants.

Because of the potential side effects that topical nasal decongestants can produce, the agency believes that, in the interest of safety, the warning proposed by the Panel in § 341.80(b)(2)(iii) for oral nasal decongestants shoul also apply to all topical nasal decongestants (except topical inhalants). Based on the Panel's review of data showing that the topical inhalants (propylhexedrine and 1-desoxyephedrine) produce little or no significant vasopressor side effects (41 FR 38402 and 38407), the agency proposes to exclude topical inhalants from this warning requirement. Therefore, in this tentative final monograph, the warning as stated in § 341.80(c)(1)(i)(*c*) "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor," will be applicable to all oral nasal decongestants, and a similar warning in § 341.80(c)(2)(iii)(*b*) "Do not use this product if you have heart disease, high blood pressure * * *" will be applicable to all topical nasal decongestants except topical inhalants. The agency also proposes to restrict the use of oxymetazoline hydrochloride and xylometazoline hydrochloride in children under 6 years of age. (See comment 28 below.)

The agency believes that the above warning and limitation of the product to 3 days use will provide for the safe use of these ingredients as OTC topical nasal decongestants.

References

(1) "AMA Drug Evaluations," 4th Ed., American Medical Association, New York, p. 454, 1960.

(2) Harvey, S.C., "Sympathomimetic Drugs," *in* "Remington's Pharmaceutical Sciences," 16th Ed., edited by A. Osol, et al., Mack Publishing Co., Easton, PA pp. 818–819, 1980.

(3) Mujic, M., and J.M. Van Rossum, "Comparative Pharmacodynamics of Sympathomimetic Imidazolines; Studies on Intestinal Smooth Muscle of the Rabbit and the Cardiovascular System of the Cat," *Archives Internationales de Pharmacodynamie et de Therapie*, 155:432–449, 1965.

(4) Copy of FDA approved labeling from NDA 11–919, in OTC Volume 04NTFM, Docket No. 76N–052N, Dockets Management Branch.

(5) Copy of FDA approved labeling from NDA 14–717, in OTC Volume 04NTFM, Docket No. 76N-052N, Dockets Management Branch.

(6) "New Drugs," American Medical Association, Chicago, pp. 211–212, 1965.

(7) "Clinical Pharmacology; Basic Principles in Therapeutics, 2d Ed., Macmillan Publishing Co., Inc., New York, p. 192, 1978.

C. Comments on Specific OTC Nasal Decongestant Active Ingredients

5. One comment stated that there is concern about camphor poisoning in children (Refs. 1 and 2) and recommended that the camphor content of OTC nasal decongestant products (topical inhalants) be limited to less than 0.75 gram (g)/30 grams (g) or to less than 2.5 percent (weight/volume). The comment stated that there is no evidence that warning statements deter childhood poisoning, but concluded that this lower concentration would reduce the risk of serious accidental poisoning while still permitting an adequate concentration of camphor.

The Panel concluded that camphor is safe when applied topically or as an inhalant at specific concentrations, but that there were insufficient data to permit final classification of its effectiveness when labeled for use as a nasal decongestant (41 FR 38406). For adults and children 2 to under 12 years of age, the Panel recommended that camphor should be used in the form of a 5-percent ointment preparation, a 7-percent solution for steam inhalation, or a lozenge containing 0.02 to 15 mg camphor. Following publication of this Panel's recommendations on camphor,

the Advisory Review Panel on OTC Miscellaneous External Drug Products (Miscellaneous External Panel) also reviewed camphor for topical use. The Miscellaneous External Panel concluded that OTC products containing a concentration of camphor greater than 2.5 percent have a low benefit-to-risk ratio and recommended that camphor be limited in OTC drug products for external use to less than 2.5 percent. The Miscellaneous External Panel also recommended that the quantity of camphor in a package be limited to a total of 360 mg per package and that camphor be marketed in a child-proof container to deter accidental poisoning of children (45 FR 63875).

In the **Federal Register** of September 21, 1982 (47 FR 41716), the agency published a final rule establishing that camphorated oil drug products (historically marketed primarily as topical counterirritants or liniments) are misbranded and are new drugs. The agency also initiated a recall of camphorated oil products to the retail level. In the **Federal Register** of September 26, 1980 (45 FR 63874), the agency announced that it was treating the data and information on camphor received from the Miscellaneous External Panel as a petition to reopen the administrative record on cold, cough, allergy, bronchodilator, and antiasthmatic drug products. The agency granted this petition by allowing those data and information to be included in the administrative record for these drug products. This notice served to inform interested persons of the existence of these recommendations and also invited persons or firms to submit any comments they may have. This reopening of the administrative record related only to the ingredient camphor in OTC drug products.

The agency's position on the safety of camphor containing products for topical application has been stated in the tentative final rule for OTC external analgesic drug products in the **Federal Register** of February 8, 1983 (48 FR 5854). In that document, the agency concluded that, at this time, there is no need to limit camphor content to 360 mg per package and that the camphor content will be limited to 11 percent or lower. The agency's position as stated in that document is hereby incorporated into this nasal decongestant rulemaking.

To date, no new data have been submitted to support the effectiveness of camphor as a nasal decongestant and at this time, camphor will remain in Category III as a nasal decongestant.

References

(1) Aronow, R.J., "Camphor Poisoning," *Journal of the American Medical Association*, 235:1260, 1976.

(2) Phelan, W.J., "Camphor Poisoning: Over-the-Counter Dangers," *Pediatrics*, 57:428–431, 1976.

6. One comment objected to the Panel's limiting eucalyptol, menthol, and thymol to lozenge and mouthwash dosage forms when these ingredients are used as "oral (topical) nasal decongestants." The comment contended that this limitation is arbitrary because viscous syrups and compressed tablets are just as effective as mouthwashes and lozenges. The comment recommended that "oral (topical) dosage" forms of eucalyptol, menthol, and thymol include any oral dosage form which is topically effective and which can be formulated to contain the same concentrations of these ingredients that are allowed for lozenges.

The comment's use of the term "oral (topical) nasal decongestant" apparently refers to dosage forms such as mouthwashes, lozenges, and compressed tablets, which are all used topically in the mouth, rather than swallowed, for a nasal decongestant effect. Compressed tablets and lozenges are solid dosage forms which can be used topically in the same manner and the site of application would be the same for compressed tablets, lozenges, and mouthwashes. The agency agrees that compressed tablets could also be included as a dosage form for eucalyptol, menthol, and thymol, when used as oral (topical) nasal decongestants intended to be dissolved in the mouth rather than swallowed, once the ingredients in this dosage form have been classified in Category I. The agency points out that eucalyptol, menthol, and thymol are all Category III ingredients, which, although found safe by the Panel, lack adequate data to demonstrate effectiveness as topical or inhalant nasal decongestants. Data to demonstrate effectiveness are required in order to permit final classification of these ingredients in the monograph for this use.

The comment's suggestion to allow viscous syrups as topical dosage forms in the mouth is not accepted because the agency is not aware of any data on viscous syrups containing eucalyptol, menthol, or thymol that are used as oral (topical) nasal decongestants. Interested persons are invited to submit data on viscous syrups containing these ingredients that are used as oral (topical) nasal decongestants in the mouth.

7. A comment representing the views of the staff of the Bureau of Consumer Protection of the Federal Trade Commission (FTC) requested that the active ingredients eucalyptol, menthol, and thymol used as a nasal decongestant or antitussive in a mouthwash dosage form be classified as Category II. The comment pointed out that after more than 4 months of adjudicative hearings, during which voluminous evidentiary records consisting of thousands of pages of expert testimony and exhibits were thoroughly examined for a marketed product with labeling and advertising claims that the product cured or prevented colds or sore throat, or lessened the severity or incidence of colds, cold symptoms, or sore thoats by killing germs (Ref. 1), the FTC determined that 0.91 mg of eucalyptol per milliliter (mL) of product (mg/mL), 0.42 mg/mL menthol, and 0.63 mg/mL thymol in a mouthwash solution are insufficient in concentration to provide relief for the symptoms of the common cold, including nasal congestion and cough. Expert medical and scientific witnesses testified that the process of gargling with a mouthwash containing these ingredients does not allow the ingredients to reach the critical areas of the body they need to reach to relieve the symptoms of a cold, nor do the ingredients penetrate the infected cells where the action of the cold viruses would be taking place.

The comment stated that the FTC's conclusion, after examining the records and hearing expert testimony, was consistent with the Panel's findings that there are no well-controlled studies documenting the effectiveness of eucalyptol, menthol, and thymol when usd in a mouthwash dosage form as a nasal decongestant or an antitussive. The comment pointed out that the FTC's opinion and supporting evidence were not available to the Panel during its deliberations. Therefore, the comment requested that the FDA review the FTC's opinion and the supporting evidence and use them as a basis to classify eucalyptol, menthol, and thymol in Category II for use as a nasal decongestant or antitussive in a mouthwash dosage form.

The response in this document addresses only the nasal decongestant use of these ingredients. The antitussive use will be addressed in a future issue of the **Federal Register.** The agency has reviewed the FTC's opinion and supporting evidence (Ref. 1). Medical and scientific experts testified at the FTC hearing that there is an absence of literature showing that the combination

of eucalyptol, menthol, and thymol in a mouthwash dosage form is effective in preventing colds and alleviating cold symptoms such as nasal congestion and cough. These experts in the fields of respiratory and infectious diseases, virology, pharmocology, and microbiology further stated, based upon their knowledge in their respective areas, that it is doubtful that these ingredients would be effective in treating symptoms of the common cold.

Although the Panel did not have access to the FTC's opinion and supporting evidence, it did review the St. Barnabas study, which was one of the studies discussed during the FTC hearing (Ref. 2). The St. Barnabas study was undertaken to demonstrate the effect of rinsing and gargling twice daily with an aqueous mixture of 0.91 mg/mL eucalyptol, 0.42 mg/mL menthol, and 0.63 mg/mL thymol on the incidence, duration, and severity of the common cold and its symptoms. It was a 4-year subjective study in over 4,800 schoolchildren. The experts who testified at the FTC hearing agreed that the deficiencies in the design and execution of the study precluded any meaningful interpretation of the results. The FTC concluded that the design and execution of the tests heavily biased the results in favor of the manufacturer, and therefore the tests could not support the advertising claims. The Panel concluded that although the study was not well-controlled and could not be considered proof of effectiveness, the results did reveal milder nasal symptoms and cough symptoms in individuals using the medicated mouthwash as compared with these symptoms in individuals using the placebo. Because this study did not demonstrate the effectiveness of the individual nasal decongestant ingredients, the Panel recommended that data to demonstrate effectiveness of each ingredient alone be required in accordance with its guidelines for testing OTC nasal decongestant drug products (41 FR 38415). Because safety was not at issue, and the data suggested the possibility that the combination of eucalyptol, menthol, and thymol was effective as a nasal decongestant in a mouthwash dosage form, the Panel believed that a Category III classification was justified.

At the tentative final monograph stage, FDA usually proposes Category II status for an ingredient only if there is a potential safety problem or if there are essentially no data to support the ingredient's effectiveness for its purported use. Although medical and scientific experts testified for the FTC that it is unlikely that eucalyptol, menthol, and thymol in a mouthwash would be effective as a nasal decongestant, they also stated that the studies that were done contained defects which made the results inconclusive. In view of the inconclusive results caused by deficiencies in the studies, the agency does not believe it appropriate at this time to classify the drugs as "ineffective," i.e., Category II, without allowing interested parties the opportunity to develop a well-controlled study that might demonstrate the drugs' effectiveness. Therefore, the agency is proposing that eucalyptol, menthol, and thymol in a mouthwash dosage form as a nasal decongestant remain in Category III in this tentative final monograph.

In the final monograph, any ingredient that has not been found to be safe and effective will be classified as "nonmonograph" and may not be legally marketed. To date, there have been no new data submitted to support the effectiveness of eucalyptol, menthol, and thymol in a mouthwash dosage form as a nasal decongestant, and if adequate data are not submitted before establishment of a final monograph, these ingredients for this use will be classified as "nonmonograph."

References

(1) Comment No. C0126, Docket No. 76N–0052, Dockets Management Branch.

(2) "The Effect of Listerine Antiseptic on the Incidence, Severity, and Duration of the Common Cold. A 4-Year Study," draft of unpublished paper in OTC Volume 040278, section 3.a. (referred to as the St. Barnabas Study in Comment No. C0126.)

8. One comment (Ref. 1) submitted new data from four controlled clinical studies (Refs. 2 through 5) on the effectiveness of 1-desoxyephedrine, alone and in combination with aromatics (camphor, menthol, methyl salicylate, bornyl acetate, and lavender oil), as a topical nasal decongestant (administered by a nasal inhaler). The comment requested Category I status for 1-desoxyephedrine based on the new data (Refs. 2 through 5), data submitted to the Panel (Refs. 6 and 7), and the manufacturer's marketing experience.

The agency has reviewed the data and concludes that they are adequate to reclassify this ingredient in Category I as a topical nasal decongestant. The combination of 1-desoxyephedrine and aromatics will be addressed in the combinations segment of the cold, cough, allergy, bronchodilator, and antiasthmatic tentative final monograph in a future issue of the **Federal Register.**

The agency's evaluation of study numbers 74–10A, 74–30, 74–58, and 70–24 (Refs. 2 through 4, and 6 and 7) showed significant decongestion of the nostrils treated with 1-desoxyephedrine and the combination of 1-desoxyephedrine and aromatics, when compared to baseline measurements or placebo. Study 75–45 (Ref. 5) showed that 1-desoxyephedrine did not cause rebound congestion within a 7-day period. Based on the data, the agency proposes an adult dosage of two inhalations in each nostril not more often than every 2 hours from an inhaler that delivers in each 800 mL of air 0.04 to 0.15 mg of 1-desoxyephedrine. In keeping with the guidelines established by the Panel (41 FR 38333), the agency proposes a dosage for children 6 to under 12 years of age of one-half of the adult dosage, i.e., one inhalation in each nostril not more often than every 2 hours from an inhaler that delivers in each 800 mL of air 0.04 to 0.15 mg of 1-desoxyephedrine. The data demonstrate that this ingredient does not cause rebound nasal congestion within a 7-day period. Therefore, the use of 1-desoxyephedrine as a topical nasal decongestant should be limited to not more than 7 days rather than the 3-day limit for other topical nasal decongestants that cause rebound congestion.

The agency's detailed comments and evaluations on the data are on file in the Dockets Management Branch (Ref. 8).

References

(1) Comment Nos. C0111, CR0003, and SUP015, Docket No. 76N–0052, Dockets Management Branch.

(2) Connell, J.T., "Nasal Decongestant Delta-'P' Method," draft of unpublished study (74–10A), in Comment No. C0111, Docket No. 76N–0052, Dockets Management Branch.

(3) Connell, J.T., "Inhaler," draft of unpublished study (74–30), in Comment No. C0111, Docket No. 76N–0052, Dockets Management Branch.

(4) Connell, J.T., "Inhaler," draft of unpublished study (74–58), in Comment No. C0111 (Volume 4), Docket No. 76N–0052, Dockets Management Branch.

(5) Connell, J.T., "Nasomucosal Rebound Delta-P," draft of unpublished study (75–45), in Comment No. C0111 (Volume 4), Docket No. 76N–0052, Dockets Management Branch.

(6) Turgeon, R.F., "Vick Inhaler," draft of unpublished study (70–24), dated February 11, 1971, in OTC Volume 040298.

(7) Memo to Burke, W.E., from E.B. Cohen, "Vick Inhaler: Vick Rhinorhemeter Study-Maine Research" (Supersedes Study 70–24 dated February 11, 1971), in OTC Volume 040298.

(8) Letter from W.E. Gilbertson, FDA, to G.F. Hoffnagle, Vicks Health Care Division of Richardson-Merrell, Inc., coded LET072, Docket No. 76N–052N, Dockets Management Branch.

9. One comment reported two cases in which use of nose drops containing phenylephrine hydrochloride had caused a permanent loss of the sense of

taste and smell. The comment recommended a warning statement in the labeling of these products which alerts consumers to the possibility of such an adverse reaction.

No data were submitted with the comment; however, the agency has reviewed both the Panel's discussion on the safety of phenylephrine hydrochloride (41 FR 38399) and its recommended warnings for nasal decongestants (41 FR 38422). The Panel concluded that phenylephrine hydrochloride is generally recognized as safe for use as a nasal decongestant, and it did not make any reference to the type of adverse reaction cited in the comment. Accordingly, no warning statement was recommeded.

The agency is concerned about the possibility of any adverse effects resulting from the use of drug products, and it routinely reviews and evaluates reports of those adverse reactions which are submitted. FDA's "Annual Adverse Reaction Summary Listing" for the period from 1969 to 1981 does include one reported case of parosmia (any disease or disorder of the sense of smell) that occurred in 1977 (Ref. 1). However, this case and the two cases cited in the comment are not adequate evidence to show a relationship between the permanent loss of the sense of taste and smell and the use of OTC nasal decongestant drops containing phenylephrine hydrochloride. Therefore, based upon the limited amount of information available on this type of adverse reaction, the agency does not consider it necessary at this time to require a warning statement, as the comment requested. The agency invites interested persons to submit additional comments and data on this type of adverse reaction.

Reference

(1) Department of Health and Human Services, Food and Drug Administration, "Annual Adverse Reaction Summary Listings," pertinent pages for the years 1969 through 1981, in OTC volume 04NTFM, Docket No. 76N–052N, Dockets Management Branch.

10. One comment questioned the studies used by the Panel to substantiate the effectiveness of phenylephrine hydrochloride as an oral nasal decongestant. The comment stated that numerous unpublished studies, which split evenly between mild successes and total failures, were quoted by the Panel, and in the one study (Ref. 1) published in an academically acceptable journal, no efficacy was seen even with doses higher than usually recommended. In addition, the comment cited two references which questioned the oral bioavailability of phenylephrine hydrochloride (Refs. 2 and 3). The comment recommended that phenylephrine hydrochloride not be used as an oral nasal decongestant.

The Panel concluded that phenylephrine hydrochloride was effective as an oral nasal decongestant after a thorough review of published and unpublished studies, oral and written submissions by manufacturers, and evaluations of clinical and marketing experience. The published study referred to by the comment (Ref. 1) is discussed in comment 11 below. The Panel was aware of one of the references that the comment cited as questioning the oral bioavailability of phenylephrine hydrochloride (Ref. 3), and cited this reference is discussing the safety of phenylephrine hydrochloride (41 FR 38399). This study is not relevant to the effectiveness of phenylephrine hydrochloride, but does confirm the potentiation of the effect of oral phenylephrine by a monoamine oxidase inhibitor.

The agency has reviewed the information cited by the comment, the Panel's recommendations, and all of the supporting data and concludes that, based on the studies cited by the Panel, information on clinical use and marketing experience, and the Panel's expertise in evaluating the clinical and marketing experience of this ingredient, there is sufficient basis to determine the phenylephrine hydrochloride is generally recognized as effective for OTC use as an oral nasal decongestant. The comment's recommendation is therefore not accepted.

References

(1) Rodgers, J.M., E.B. Reilly, and H.A. Bickerman, "Physiologic and Pharmacologic Studies on Nasal Airway Resistance," *Clinical Pharmacology and Therapeutics*, 14:146, 1973.

(2) Innes, I.R., and M.L. Nickerson, "Norepinephrine, Epinephrine, and the Sympathomimetic Amines," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L.S. Goodman and A. Gilman, the Macmillan Co., New York, pp. 477–494, 1975.

(3) Elis, J., et al., "Modification by Monoamine Oxidase Inhibitors of the Effect of Some Sympathomimetics on Blood Pressure," *British Medical Journal*, 2:75–78, 1967, in OTC Cough/Cold Reference Volume E, Docket No. 76N–0052, Dockets Management Branch.

11. One comment stated that a reference to a study by Rodgers, Reilly, and Bickerman (Ref. 1) cited by the Panel in three different places (in part VIII. paragraph B.d. on page 38400, in part VIII. paragraph B.e. on page 38401, and in part VIII. paragraph B.h. on page 39403) was incorrect in that the cited information was not contained in that particular reference.

The agency has reviewed the Panel's discussions on pages 38399 through 38403 and agrees with the comment that the study by Rodgers, Reilly and Bickerman (Ref. 1) does not contain the information cited by the Panel on page 38399, nor is the agency aware of what reference should have been cited there. Nevertheless, this omission does not have a bearing on the tentative status of phenylephrine hydrochloride for oral and topical use as a nasal decongestant.

The agency has determined, however, that the information in the discussions on pages 38401 and 38403 is supported in another study by Bickerman (Ref. 2) that was reviewed by the Panel and cited on page 38401. The information on pages 38401 and 38403 that was attributed to the study by Rodgers, Reilly, and Bickerman (Ref. 1) should be attributed to the Bickerman Study (Ref. 2).

References

(1) Rodgers, J.M., E.B. Reilly, and H.A. Bickerman, "Physiologic and Pharmacologic Studies in Nasal Airway Resistance," (abstract). *Clinical Pharmacology and Therapeutics*, 14:146, 1973.

(2) Bickerman, H.A., "Physiologic and Pharmacologic Studies on Nasal Airway Resistance (R^N). Current Research Methodology in the Evaluation of Proprietary Medicines, Cold and Allergy Preparations," *in* "Conference Proceedings of the Research and Scientific Development Committee of the Proprietary Association," The Proprietary Association, New York, pp. 60–72, 1971.

12. One comment claimed that certain OTC inhalant nasal decongestant products containing propylhexedrine have the capability of producing a "high" and therefore have a potential for abuse. The comment included a 1976 newspaper article which described six deaths traced to the abuse of propylhexedrine.

The Panel reviewed the data submitted on propylhexedrine and concluded that it was safe and effective for OTC use (41 FR 38402). In the dosage range recommended by the Panel, propylhexedrine has a wide margin of safety and relative freedom from toxic effects. Harvey (Ref. 1) describes propylhexedrine as a volatile indirect sympathomimetic amine that does not have central excitatory effects or addiction liability. It has a decongestant effect on the nasal mucous membrane and acts as a vasoconstrictor when inhaled once or twice through each nostril. It is considered safe for self-medication by adults, but children should not have unsupervised access to

a propylhexedrine inhaler. Side effects of propylhexedrine include rebound congestion, headache, and, in rare instances, an increase in blood pressure (Ref. 1). The Panel pointed out that 100 mg oral doses of propylhexedrine alone induce a 17- to 23-millimeter (mm) rise in blood pressure and reflex bradycardia in normal adults but no overt symptoms or euphoria, palpitation, or dry mouth (41 FR 38402).

The agency agrees with the Panel's conclusion that propylhexedrine has a wide margin of safety in the dosage range recommended for use by adults and children 6 to under 12 years of age (0.40 to 0.50 mg in two inhalations per nostril). The Panel pointed out that "the risk of misuse and/or abuse is minimized by restriction on the types of pharmacologic agents in available OTC products, limitations on dosage and concentration of active drug, and adequate and explicit directions for use coupled with appropriate warnings" (41 FR 38332).

The agency routinely reviews and evaluates reports of adverse reactions resulting from the use of OTC drug products. Annual adverse reaction summaries, compiled for the years 1969 to 1981 (Ref. 2), show that, of 21 cases of adverse reactions reported during this 12-year period for the two products mentioned by the comment, 7 cases involved the misuse of propylhexedrine in an inhaler. The six propylhexedrine-related deaths referred to by the comment occurred among individuals, most of whom had a history of drug abuse, who knowingly misused the drug. The agency is concerned about the possibility of any adverse effects resulting from the use of OTC drug products, but it also recognizes that a number of substances in the marketplace can be and are abused by some individuals. The few isolated reports on the abuse of propylhexedrine (the latest one was reported to the agency in 1977) do not indicate a widespread problem. The agency believes that propylhexedrine should be available as an inhalant nasal decongestant because it is safe and effective, when used as instructed in the labeling.

References

(1) Harvey, S.C., "Sympathomimetic Drugs," *in* "Remington's Pharmaceutical Sciences," 16th Ed., edited by A. Osol, et al., Mack Publishing Co., Easton, PA, p. 830, 1980.

(2) Department of Health and Human Services, Food and Drug Administration, "Annual Adverse Reaction Summary Listing," pertinent pages for the years 1969 through 1981, in OTC Volume 04NTFM, Docket No. 76N-052N, Dockets Management Branch.

13. Several comments strongly disagreed with the Panel's recommendation that pseudoephedrine preparations be available OTC as nasal decongestants. One comment agreed with the Panel's recommendation. The comments that objected to the OTC status of pseudoephedrine stated that pseudoephedrine causes tachyphylaxis fatigue of the beta-response mechanism and urinary retention; side effects, although rarely severe or fatal, occur frequently; pseudoephedrine is a stimulant and overuse may be very damaging; and unrestricted availability to the public may be dangerous.

The agency agrees with the Panel's recommendation that pseudoephedrine preparations (pseudoephedrine hydrochloride and pseudoephedrine sulfate) are safe and effective as oral nasal decongestants for OTC use. The comments did not submit any data in support of their reasons for objecting to the OTC status of pseudoephedrine.

It has been reported in the literature that tachyphylaxis, a condition in which effectiveness of a drug decreases after rapidly repated doses, can occur with ephedrine and its isomeric forms (i.e., d- and l-ephedrine, and d- and l-pseudoephedrine) (Refs. 1, 2, and 3). However, the agency concludes that this should not be a problem if the drug is used according to labeling directions.

Roth et al. (Ref. 4) reported that side effects of patients treated with a single oral dose of 60 mg of pseudoephedrine were minimal. Of 30 patients, 2 experienced mild elevations in pulse rate, 1 developed a moderate elevation in pulse rate, 1 experienced mild elevations in pulse rate and diastolic blood pressure, 1 developed palpitations and a slight increase in pulse rate, 2 reported tiredness, and 3 reported a light-headed feeling. Empey et al. (Ref. 5) noted that side effects were of little problem in patients taking 60 mg of pseudoephedrine three times a day. In this study, pseudoephedrine and an antihistamine were tested separately, in combination, and compared with a placebo. One patient reported dryness of the mouth when taking pseudoephedrine alone, and one patient reported excessive sweating, but there were no reports of nervousness or palpitations. The authors stated that the lower incidence of drowsiness reported with the combination, as compared with the antihistamine alone, might reflect a slight stimulant effect from pseudoephedrine; however, stimulation was not reported by anyone taking pseudoephedrine alone. In its report, the panel cited a study which indicated that mild side effects, such as drowsiness, nausea, insomnia, and headache, can occur with the use of pseudoephedrine (Ref. 6). However, these side effects are not severe and would not warrant the elimination of pseudoephedrine from the OTC marketplace. Pseudoephedrine preparations have been marketed OTC safely for many years.

The use of pseudoephedrine, as with most other sympathomimetic drugs, may cause an increase in blood pressure when taken with monoamine oxidase inhibitors. Therefore, the Panel recommended a drug interaction precaution for oral nasal decongestants in § 341.80(b)(2)(iv) (redesignated as § 341.80(c)(1)(i)(*d*) in this tentative final monograph) to warn against the use of the product when taking a prescription drug for high blood pressure or depression without first consulting a doctor. (See comment 23 below.)

Because of the vasoconstrictive properties of sympathomimetic drugs, persons suffering from urinary retention, especially elderly men with an enlarged prostate, could experience increased difficulty in urinating (Refs. 7 and 8). Males with an enlargd prostate shoud only use these drugs under the supervision of a physician. Therefore, the agency has determined that this condition will be added to the warning proposed by the Panel in § 341.80(b)(2)(iii) which appears as § 341.80(c)(1)(i)(*c*) in this tentative final monograph. This warning will read as follows: "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor." (NOTE: The part of the warning concerning "difficulty in urination due to enlargement of the prostate gland" is not necessary for products labeled for use only in children under 12 years of age. That part of the warning is not applicable to children and its presence in the labeling would tend to distract parents from label warnings which are important. Accordingly, the revised warning for products labeled for use in children only, "Do not give this product to children who have heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor," has been added to the tentative final monograph in § 341.80(c)(1)(ii)(c)). The directions for use and appropriate warnings will inform the consumer of the proper use of the product. Based on these considerations, the agency concludes that pseudoephedrine will remain available as an OTC nasal decongestant.

References

(1) Innes, I.R., and M. Nickerson, "Norepinephrine, Epinephrine, and the Sympathomimetic Amines," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L.S. Goodman and A. Gilman, Macmillan Publishing Co., New York, pp. 500–501, 1975.

(2) Patil, P.N., A. Tye, and J.B. Lapidus, "A Pharmacological Study of the Ephedrine Isomers," *Journal of Pharmacology and Experimental Therapeutics*, 148:158–168, 1965.

(3) Aviado, D.M., Jr., A.L. Wnuck, and E.J. DeBeer, "Cardiovascular Effects of Sympathomimetic Bronchodilators, Epinephrine, Ephedrine, Pseudoephedrine, Isoproterenal, Methoxyphenamine and Isoprophenamine," *Journal of Pharmacologh and Experimental Therapeutics*, 122:406–417, 1958.

(4) Roth, R.P., et al., "Nasal Decongestant Activity of Pseudoephedrine, "*Annals of Otology, Rhinology and Laryngology*, 86:235–241, 1977.

(5) Empey, M.B., et al., "A Double-Blind Crossover Trial of Pseudoephedrine and Triprolidine Alone and in Combination, for the Treatment of Allergenic Rhinitis," *Annals of Allergy*, 34:41–46, 1975.

(6) Arbesman, C.E., and R.J. Ehrenreich, "New Drugs in the Treatment of Allergies," *New York State Journal of Medicine*, 61:219–299, 1961.

(7) Innes, I.R., and M. Nickerson, "Norephinephrine, Epinephrine, and the Sympathomimetic Amines," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L.S. Goodman and A. Gilman, Macmillan Publishing Co., New York, pp. 505–507, 1975.

(8) Harvey, S.C., "Sympathomimetic Drugs," *in* "Remington's Pharmaceutical Sciences," 16th ED. edited by A. Osol, et al., Mack Publishing Co., Easton, PA, pp. 818–820, 1980.

D. Comments on Dosages for OTC Nasal Decongestants

14. One comment stated that there was an inconsistency between the dosage for naphazoline hydrochloride recommended by the Panel in § 341.20(b) and the warning for that ingredient in § 341.80(b)(6). The comment explained that in § 341.20(b) there is no dosage instruction for the use of a 0.05-percent solution in children under 12 years of age. However, § 341.80(b)(6) states that the 0.05-percent solution is not to be given to children under 6 years of age. Because the ages 6 to under 12 years are not mentioned in § 341.80(b)(6), the comment recommended that the warning in § 341.80(b)(6) should state that the 0.05-percent solution is not to be given to children under 12 years of age or, as an alternative, that dosage instructions for the 0.05-percent solution for children 6 to 11 years of age be included in § 341.20(b).

The agency agrees that the warning recommended by the Panel in § 341.80(b)(6) should be revised for clarity. The dosage instructions as stated in § 341.20(b) specify that 0.05 percent naphazoline hydrochloride is for adult use only, and that a 0.025-percent solution is to be used for children 6 to under 12 years of age. However, the warning in § 341.80(b)(6) states that the 0.05-percent solution is for adult use and should not be used in children under 6 years of age. As the comment points out, the warning in § 341.80(b)(6) neglects to mention children in the 6- to under 12-year age group. In § 341.3(a) of the advance notice of proposed rulemaking (41 FR 38419), an adult has been defined as any person 12 years of age and older. The agency has deleted the first part of the Panel's warning in § 341.80(b)(6), "For adult use only," because the product directions will specify that the 0.05-percent solution should be used only in adults. Therefore, the warning in § 341.80(b)(6) (redesignated as § 341.80(c)(2)(iv) in this document) will be revised to read as follows:

For products containing naphazoline hydrochloride identified in § 341.20(b)(6) at a concentration of 0.05 percent: "Do not use this product in children under 12 years of age because it may cause sedation if swallowed."

15. One comment proposed that § 341.20(d)(2) be revised so that an "aqueous solution" is not specified in the formulation of phenylephrine hydrochloride as a topical nasal decongestant. The comment stated that all other portions of the monograph avoid specifying inactive ingredients and that specifying an inactive ingredient was not consistent with the intent of the OTC drug review. The comment also stated that if an "aqueous solution" was specified in the formulation of phenylephrine hydrochloride to assure against the potential problem of lipid pneumonia, which can occur from the accidental aspiration of oil-based nose drops, then an appropriate limitation should be incorporated into the monograph to protect against this possibility. The comment suggested limiting the product form to "non-oil-based drops or sprays."

The purpose of the OTC drug review process is to determine the safety and effectiveness of OTC drugs. If an active ingredient is safe, but the product's inactive ingredient formulation results in an unsafe product, it was the responsibility of the Panel to address those ingredients which make the product unsafe. As the comment observes, oil-based drops or sprays may be aspirated into the lungs and may cause lipid pneumonia (Refs. 1 and 2). The Panel recognized this problem and concluded that nasal drops and sprays can only be generally recognized as safe and effective for OTC use when they are formulated as aqueous solutions. Because the designation "non-oil-based" solutions could also include types of solutions that are non-aqueous, the agency believes that a more explicit term than "non-oil-based" is necessary. Therefore, the comment's suggestion is not accepted. The phrase "aqueous solution" will remain in the topical nasal decongestant dosage for drops and sprays in § 341.20(a), (b), (c), (d)(2), and (h) (redesignated as § 341.80(d)(2)(ii)(*a*), (iii)(*a*), (iv)(*a*), and (vii)(*a*) in this document).

References

(1) Crofton, J., and A. Douglas, "Respiratory Diseases," Blackwell Scientific Publications, Oxford, England, pp. 142–150, 1969.

(2) Martin, E.W., "Hazards of Medication," 2d Ed., J.B. Lippincott Co., Philadelphia, pp. 206–207, 1978.

16. One comment (Ref. 1) stated that the Panel's recommended dosage of phenylephrine hydrochloride in § 341.20(d)(2) inadvertently allows an unnecessarily wide variation in dosage and unnecessarily restrains product formulation. The dosage allowed by the Panel is two or three sprays per nostril of a 0.25 to 0.5 percent aqueous solution. The comment stated that no effort was made to define the quantity of drug that is to be delivered in each spray; that the amount of drug delivered by a spray container can vary significantly from one container to another depending on the design and dimensions of the nozzle orifice; that container shape and fill-level also affect the amount of product delivered; that the Panel's recommendation does not limit the drug delivery system to a spray container like the one currently in common use and as a result any kind of spray mechanism could be used with even greater variability. The comment added that for all drugs in the monograph, except topical nasal decongestants, the dosages are given in concise statements of the quantity of drug to be delivered and requested that manufacturers should be permitted to formulate at percentages below 0.25 or above 0.50 as long as the total drug delivery is within the dosage range proposed by the comment. The comment submitted data to support a dosage range of 0.80 to 1.80 mg of phenylephrine hydrochloride per nostril every 4 hours.

The comment raises a number of valid points. The dosages recommended for nasal drops and sprays are not absolute amounts and are variable; however, the

Panel reviewed numerous studies on nasal drops and sprays which showed that there is a wide range of safety with these drugs. Nasal sprays and drops have been available for years, and the data that have been accumulated on these products show that the concentrations and dosages recommended by the Panel are safe and effective. Thus, although there may be some variation in the amount of drug delivered from various droppers or spray containers, the amount of drug delivered will be within the safe and effective range. The study submitted by the comment was designed to quantitatively determine the amount of phenylephrine hydrochloride delivered with one spray from a commercial nasal spray squeeze bottle. The data did not show that the measured amount of drug was either a safe or effective dose. The comment's suggestion for a milligram dosage is not accepted, and dosages for nasal drops and sprays will continue to be defined in terms of concentration.

Reference

(1) Comment No. C0135, Docket No. 76N-0052, Dockets Management Branch.

17. One comment requested that 1 percent phenylephrine hydrochloride for OTC use as a topical nasal decongestant be placed in Category I as safe and effective. The comment pointed out that the Panel recommended Category I status for aqueous solutions of phenylephrine hydrochloride in concentrations of 0.125, 0.25, and 0.5 percent. Although a submission on 1 percent phenylephrine was made, the Panel did not categorize this concentration. Two studies were submitted with the comment to document the safety and effectiveness of 1 percent phenylephrine hydrochloride (Ref. 1). The comment pointed out that nasal decongestant drops containing 1 percent phenylephrine hydrochloride have been marketed OTC for 40 years.

The agency has reviewed the two studies submitted to support the comment's request to place 1 percent phenylephrine hydrochloride in Category I for OTC use as a topical nasal decongestant. The results of the studies showed no significant difference in effectiveness between 0.5 and 1 percent concentrations of phenylephrine hydrochloride. Nasal irritation and side effects such as headache, nausea, dizziness, nasal edema, and erythema occurred with both 0.5 and 1 percent concentrations; but the differences in side effects between the two groups were not statistically significant. However, the data did suggest that the 1-percent concentration seemed more likely to induce rebound congestion. Therefore, the agency is proposing that 1 percent phenylephrine hydrochloride be classified in Category I as a topical nasal decongestant and that the product be labeled for adult use only. Additionally, because of a possible rebound effect with continued use of the 1-percent concentration of phenylephrine hydrochloride, the agency is proposing the following warning in § 341.80(c)(2)(v) for the 1-percent concentration of phenylephrine hydrochloride, "Frequent use of this product may cause nasal congestion to recur or worsen."

The agency's detailed comments and evaluation on the data are on file in the Dockets Management Branch (Ref. 2).

Reference

(1) Comment No. C0125, Docket No. 76N-0052, Dockets Management Branch.

(2) Letter from W.E. Gilbertsen, FDA, to E.J. Hiross, Sterling Drug, Inc., coded LET081, Docket No. 76N-052N, Dockets Management Branch.

18. Several comments agreed with the Panel's recommendation to make 60 mg pseudoephedrine preparations available on an OTC basis. (Previously, oral nasal decongestants containing 60 mg pseudoephedrine were available only on a prescription basis. Preparations containing 30 mg pseudoephedrine have been available on an OTC basis for many years.) However, two of the comments expressed concern over the 24-hour dosage limit of 360 mg for pseudoephedrine preparations recommended by the Panel. Both of these comments recommended a dosage of 60 mg pseudoephedrine every 4 to 6 hours for a maximum of 240 mg per 24 hours rather than the 60 mg every 4 hours not to exceed a maximum of 360 mg in 24 hours recommended by the Panel. Because the maximum daily dose for the prescription 60-mg pseudoephedrine preparations was 240 mg per 24 hours, the comments argued that it does not seem reasonable to recommend a 360-mg maximum daily dose for OTC pseudoephedrine preparations.

One of the comments submitted data on the pharmacokinetics of pseudoephedrine, indicating that a 240-mg maximum dose per 24 hours may be a more appropriate dose for OTC use of 60-mg pseudoephedrine preparations (Ref. 1). In addition, information was submitted from a study showing that increasing the 24-hour dosage to 360 mg did not present a clinical advantage. The comment concluded that the risk-to-benefit ratio favors limiting the dosage to 240 mg per day.

The agency concluded from these comments and data that a dosage of 60 mg of pseudoephedrine every 4 hours might lead to accumulation of the drug and eventually marked side effects, and that a daily dosage in excess of 240 mg might be associated with significant side effects without additional therapeutic benefit. Therefore, the agency published a notice in the **Federal Register** of September 30, 1980 (45 FR 64709) changing the dosage of pseudoephedrine to 60 mg every 6 hours with a maximum 24-hour dose of 240 mg.

Three drug manufacturers subsequently submitted a petition containing new data to prove that if a 240-mg/24-hour limit is observed, a dosing interval of every 6 hours confers no added safety benefit relative to a more flexible interval of every 4 to 6 hours (Ref. 2). The petition included information on the pharmacokinetic behavior of pseudoephedrine, a review of adverse drug reactions related to pseudoephedrine, and eight studies (Refs. 3 through 10). The companies supported reduction of the maximum adult dosage of pseudoephedrine from 360 to 240 mg in 24 hours, but requested that the agency adopt a dosage interval of 60 mg every 4 to 6 hours. The petitioners also requested an extension of the May 1, 1981 effective data for compliance with the revised dosage limitations that had been set forth in the September 30, 1980 notice. In the **Federal Register** of May 5, 1981 (46 FR 25144), the agency stayed until further notice the May 1, 1981 effective date for the revised dosage interval of 60 mg every 6 hours until the new data had been reviewed. The requirement for revised labeling reflecting the maximum daily OTC dosage of 240 mg for adults and corresponding maximum daily OTC dosages for children was not stayed, but became effective on May 1, 1981.

The agency has determined that the pharmacokinetic data show that the major determinant of the half-life of pseudoephedrine is urinary pH and that the half-life varies from 4 to 8 hours in normal individuals who are representative of the population at large. The agency notes that only two of the eight studies are relevant to the issue of whether the frequency of administration of pseudoephedrine is a factor in the incidence of side effects (Refs. 3 and 4). The Kuntzman study (Ref. 3) demonstrates the influence of urinary pH on the half-life of pseudoephedrine. When urinary pH is decreased, plasma half-life of pseudoephedrine is decreased markedly. In contrast, when urinary pH is increased, plasma half-life increases. The Brater study (Ref. 4)

confirms Kuntzman's findings. After reviewing the new data, the agency finds that there is sufficient evidence to show the efficacy of a total daily dose of 240 mg of pseudoephedrine and that it is reasonable to project similar plasma levels, whether this total daily dose is given as 60 mg every 4 to 6 hours or as 60 mg every 6 hours. The agency, therefore, agrees with the comment that a more flexible adult dosage schedule for pseudoephedrine of 60 mg every 4 to 6 hours, not to exceed 240 mg daily, should be permitted. The dosage and directions for use of pseudoephedrine in § 341.80(d) (1) (ii) of the tentative final monograph will reflect this proposed revision. The dosages for children will also reflect the proposed change in dosage interval. The agency's comments on the data are on file in the Dockets Management Branch (Ref. 11).

References

(1) Comment No. C0112, Docket No., 76N–0052, Dockets Management Branch.

(2) Citizen Petition, Docket No. 76N–052N, Dockets Management Branch.

(3) Kuntzman, R.G., et at., "The influence of urinary pH on the plasma half-life of pseudoephedrine in man and dog and a sensitive assay for its determination in human plasma." *Clinical Pharmacology and Therapeutics,* 12:62–67, 1971, in Citizen Petition, Docket No. 76N–052N, Dockets Managment Branch.

(4) Brater, D.C., et al., "Renal excretion of pseudophedrine," *Clinical Pharmacology and Therapeutics,* 28:690–694, 1980, in Citizen Petition, Docket No. 76N–052N, Dockets Management Branch.

(5) Roth, R.P., et al., "Nasal Decongestant Activity of Pseudoephedrine," *Annals of Otology, Rhinology and Laryngology,* 86:235–242, 1977, in Citizen Petition, Docket No. 76N–052N, Dockets Managmeent Branch.

(6) Jacobi, A., et al., "Evaluation of Sustained-Action Chlorpheniramine-Pseudoephedrine Dosage Forms in Humans," *Journal of Pharmaceutical Sciences,* 69:1077–1081, 1980, in Citizen Petition, Docket No. 76N–052N, Dockets Management Branch.

(7) Bright, T.P., et al., "Selected Cardiac and Metabolic Responses to Pseudoephedrine with Exercise," draft of unpublished study from Dow Chemical Co., in Citizen Petition, Docket No. 76N–052N, Dockets Management Branch.

(8) Empey, D.W., et al., "Dose-Response Study of the Nasal Decongestant and Cardiovascular Effects of Pseudoephedrine," *British Journal of Clinical Pharmacology,* 9:351–358, 1980, in Citizen Petition, Docket No. 76N–052N, Dockets Management Branch.

(9) Bye, Co., et al., "A Comparison of Plasma Levels of L (+) Pseudoephedrine Following Different Formulations, and their Relation to Cardiovascular and Subjective Effects in Man," *European Journal of Clinical Pharmacology,* 8:47–53, 1975, in Citizen Petition, Docket No. 76N–052N, Dockets Management Branch.

(10) Perkins, J.G., "A Bioavailability and Safety Study Comparing Actifed® Sustained-Action (SA) Capsules to Actifed Immediate-Release (IR) Tablets," *Current Therapeutic Research,* 28:650–668, 1980, in Citizen Petition, Docket No. 76N–052N, Dockets Management Branch.

(11) Letters from W.E. Gilbertson, FDA, to K.V. Crean, Buroughs-Wellcome Co., A.S. Davidson, Schering Corp., and R.L. Selman, Dow Chemical Co., coded LET077, LET078, and LET079, Docket No. 76N–052N, Dockets Management Branch.

19. One comment suggested deleting from § 341.20(c), § 341.20(d)(2), and § 341.20(h) of the Panel's recommendations the provision that topical nasal decongestant drug products containing oxymetazoline hydrochloride, phenylephrine hydrochloride, or xylometazoline hydrochloride, when administered to children 2 to under 6 years of age, should be used only in the form of nose drops and not in the form of nasal sprays. The comment stated that the Panel based this provision on the contention that a spray is difficult to use in a small nostril. The comment argued that while there may be a problem if the same nosepiece is used for both adult's and children's sprays, this problem could be resolved by using a nosepiece especially designed for the smaller nostril of children 2 to 6 years of age.

As noted in the comment, the only reason given in the Panel's report for not permitting the use of nasal decongestant sprays in children 2 to under 6 years of age is that "the spray is difficult to use in the small nostril" (41 FR 38420). The agency agrees with the comment that manufacturers should be permitted to modify the nosepiece of a nasal decongestant spray so that it can be used in a small nostril. The agency also believes that the use of a nasal spray in certain instances may be easier and more acceptable than the use of drops, especially when the obvious problems of administering drops to children in the 2- to under 6-year age range are taken into consideration.

Nasal decongestant ingredients such as phenylephrine hydrochloride have been marketed OTC for use in children in a nasal spray dosage form for many years without reports of significant adverse reactions directly attributable to the use of the spray (Ref. 1) However, the agency has concluded that oxymetazoline hydrochloride and xylometazoline hydrochloride should not be used in children under 6 years of age in any dosage form. These drugs are long-acting, potent vasoconstrictors and can cause side effects. It is often difficult to measure a correct dose of a topical nasal decongestant in a small child, and the child may inadvertently receive an excessive dose by swallowing the administered medication. Therefore, the agency believes that in the interest of safety, oxymetazoline hydrochloride and xylometazoline hydrochloride should not be used in children under 6 years of age unless directed by a doctor. (See comment 29 below.) The statement recommended by the Panel in § 341.20(c), (d)(2), and (h) "Only drops should be used in children 2 to under 6 years since the spray is difficult to use in the small nostril" will not be included in this tentative final monograph. The agency is proposing that the dosage instruction for the use of oxymetazoline hydrochloride and xylometazoline hydrochloride in children under 6 years of age be deleted from § 341.20 (c) and (h) and placed in professional labeling in § 341.90 (m) and (n). The directions for phenylephrine hydrochloride in § 341.80(d)(2)(v)(4) of this tentative final monograph have been revised to include the use of drops or sprays for children 2 to under 6 years of age.

Additionally, the Panel did not address topical nasal decongestants in a jelly dosage form, although these products are presently marketed. The agency has concluded that a jelly should not be used in children under 6 years of age. A jelly must be placed in the nose and then inhaled well back into the nasal passages. The small nostril of a child under 6 years of age could make insertion of a proper amount of nasal decongestant jelly very difficult, and a safe or effective dose may not be achieved. Other topical dosage forms, such as sprays or drops would be more acceptable for use by a child under 6 years of age. Therefore, for children under 6 years of age, the agency is restricting the use of any topical nasal decongestant formulated as a jelly unless directed by a doctor. This restriction has been added to the appropriate "Directions" sections of the monograph.

Reference

(1) Department of Health and Human Services, Food and Drug Administration, "Annual Adverse Reaction Summary Listing," pertinent pages for the years 1969 through 1981, in OTC Volume 04NTFM, Docket No. 76N–052N, Dockets Management Branch.

E. Comments on OTC Nasal Decongestant Labeling and Warnings

20. One comment urged that every manufacturer of a nasal decongestant drug product be required to label the product as a "nasal decongestant" instead of as a "decongestant" as many such products are labeled. Also, the comment pointed out that the consumer

often mistakenly thinks that decongestant means expectorant and therefore may self-medicate with the wrong drug.

The agency agrees that a nasal decongestant drug product should be clearly labeled as such instead of simply as a "decongestant". Under § 341.80(a) of this tentative final monograph, nasal decongestant drug products would be required to use the term "nasal decongestant" as the statement of identity.

21. Several comments pointed out that OTC drug products containing oral nasal decongestants may be labeled and marketed for use only in pediatric populations. The comments argued that the warning statement proposed by the Panel, i.e., "Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor . . .," applies only to adults and should not be required on products labeled strictly for use in children. The comments recommended that an exempting statement should be added to the monograph under § 341.50(c) stating, "Warnings which are inappropriate for children's products may be eliminated in the labeling of products containing dosage instructions for children only."

The agency does not agree that the drug interaction precaution recommended by the Panel in § 341.80(b)(2)(iv) concerning prescription antihypertensives and antidepressants containing a monoamine oxidase inhibitor should be deleted from the labeling of pediatric products. Hypertension and depression do occur in children (Refs. 1, 2, and 3). Pediatric dosages for antihypertensives are provided in a widely recognized pediatric text; however, antidepressants containing a monoamine oxidase inhibitor are not widely accepted for pediatric use and pediatric dose ranges have not been established (Refs. 4 and 5). Nevertheless, a physician might prescribe either of these drugs for children. Accordingly, this drug interaction warning will be required in the labeling of all oral nasal decongestants. (Note: The agency is proposing to simplify this warning statement, which will appear in this document as § 341.80(c)(1)(i)(*d*), to read as follows: "*Drug interaction precaution.* Do not take this product if you are presently taking a prescription drug for high blood pressure or depression, without first consulting your doctor." (See comment 22 below.))

The agency is not adding an exempting statement to the monograph as suggested by the comment. However, a portion of one warning concerning "difficuly in urination due to enlargement of the prostate gland" has been deleted for products labeled for use in children only (see comment 13 above). Additionally, warnings for products which are labeled specifically for children 2 to under 12 years of age have been reworded to reflect the administration of the products by adults rather than self administration. Warnings for products which are labeled for both adults and children have also been proposed in the tentative final monograph.

References

(1) Loggie, J.M.H., "Hypertension," *in* "Textbook of Pediatrics," edited by W.E. Nelson, 11th Ed., W.B. Saunders Co., Philadelphia, pp. 1353–1361, 1979.

(2) Forman, M.A., W.H. Hetznecker, and J.M. Dunn, "Psychopharmacology," *in* "Textbook of Pediatrics," edited by W.E. Nelson, 11th Ed., W.B. Saunders Co., Philadelphia, pp. 93–95, 1979.

(3) Etteldorf, J.N., "Noninfectious Disorders of the Urinary System," *in* "Pediatric Therapy," 4th Ed., edited by H.C. Shirkey, C.V. Mosby Co., St. Louis, pp. 722–725, 1972.

(4) Shirkey, H.C., "Table of Drugs," *in* "Pediatric Therapy," 4th Ed., edited by H.C. Shirkey, C.V. Mosby Co., St. Louis, pp. 1150–1152, 1972.

(5) Rapoport, J.L., and E. Mikkelsen, "Antidepressants," *in* "Pediatric Psychopharmacology: The Use of Behavior Modifying Drugs in Children," edited by J.S. Werry, Brunner/Mazel, New York, pp. 208–233, 1978.

22. Two comments suggested that the Panel's recommended drug interaction precaution for oral nasal decongestant drug products should be deleted from § 341.80(b)(2)(iv) of the monograph. This precaution is "Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor except under the advice and supervision of a physician." One comment argued that terms such as "antihypertensive," "antidepressant," and "monoamine oxidase inhibitor" are highly technical; that only a small percentage of the population is likely to understand this warning; and that including such a warning in the labeling of an OTC drug is contrary to the well-established principle that unnecessary or confusing precautions tend to dilute the significance of all instructions in the labeling and, hence, should be avoided. The other comment contended that it is the responsibility of the physician to instruct each patient who is taking a monoamine oxidase inhibitor on the proper means of avoiding the possible adverse reactions that can be associated with the use of this type of drug.

The agency agrees with the comment that the Panel's proposed drug interaction precaution may not be readily understood by all consumers. However, it considers a warning of this type necessary to alert consumers because antihypertensive and antidepressant drugs are widely prescribed. To simplify this precautionary statement the agency is proposing to substitute the term "high blood pressure" for the term "antihypertensive" and the term "depression" for "antidepressant." The agency also believes that the words "monoamine oxidase inhibitor" would be confusing to consumers and need not be included in the precautionary statement to convey the intended message. Accordingly, § 341.80(b)(2)(iv) (redesignated in this tentative final monograph as § 341.80(c)(1)(i)(*d*)) will be amended to read as follows: "*Drug interaction precaution.* Do not take this product if you are presently taking a prescription drug for high blood pressure or depression, without first consulting your doctor."

23. Two comments stated that the claim "relieves sinus pressure" should be in Category I rather than in Category III. One comment (Ref. 1) submitted the results of a survey conducted among sinus headache sufferers who were asked about the nature of their symptoms, i.e., whether facial pressure and/or facial congestion were present. Of 428 respondents who mentioned facial pressure 65.9 percent also mentioned facial congestion; of 380 respondents who mentioned facial congestion, 74.2 percent also mentioned facial pressure; and 704 (72.5 percent) of 971 patients taking medication to relieve the congestion of sinus headache also expected it to relieve sinus pressure. The comment concluded that consumers use the term "pressure" synonymously with "congestion." The second comment stated that the Panel's recommendations are conflicting because the Panel placed in Category I those claims relating to the relief of congestion and the promotion of sinus drainage. However, claims relating to relief of sinus pressure were placed in Category III. The comment did not submit any data in support of its position but concluded that it is a simple fact that relief of congestion and promotion of sinus drainage will relieve sinus pressure.

The agency has reviewed the survey data, including a statistical evaluation (Ref. 1), to determine whether the data support the comment's contention that "congestion" and "pressure" are synonymous terms to consumers. The details of the survey are insufficient to

support any definitive conclusions. However, it seems likely that the terms "sinus pressure" and "sinus congestion" are closely associated in the minds of consumers. "Webster's New Collegiate Dictionary" (Ref. 2) defines "pressure" as "the application of force to something by something else in direct contact with it." "Congestion" is defined as "[concentration] in a small or narrow space" (Ref. 3). "Congestion" is also defined as "excessive or abnormal accumulation of blood in a part" (Ref. 4). Using these definitions, it would follow that congestion is logically thought to be the cause of pressure. If an area (e.g., the sinuses) is congested, then whatever is causing the congestion is likely to exert pressure on the boundaries of the area. It would then follow that if congestion were relieved, pressure would be relieved also. Therefore, the agency has decided to expand the Category I indications for nasal decongestants proposed by the Panel in § 341.80(a)(9) and (10) (redesignated as § 341.80(b)(2) (iv) and (v) in this tentative final monograph). The revised indications will read as follows:

(iv) "Helps decongest sinus openings and passages; relieves sinus pressure."

(v) "Promotes nasal and/or sinus drainage; relieves sinus pressure."

References

(1) Comment No. C0056, Docket No. 76N–0052, Dockets Management Branch.

(2) "Webster's New Collegiate Dictionary," G.&C. Merriam Co., Springfield, MA, 1979, s.v. "pressure."

(3) "Webster's New Collegiate Dictionary," G.&C. Merriam Co., Springfield, MA, 1979, s.v. "congestion."

(4) "Dorland's Illustrated Medical Dictionary," 25th Ed., W.B. Saunders Co., Philadelphia, 1974, s.v. "congestion."

24. Several comments objected to the Panel's recommended warning in § 341.80(b)(ii) for topical nasal decongestants: "Do not use this product for more than 3 days . . . ." The comments contended that rebound congestion does not begin to appear until more than 7 days after starting use, that the basis for the warning is the assumption that the product will not be used according to label directions, and that the Panel cited no data to support the 3-day limitation. The comments added that "AMA Drug Evaluations" (Ref. 1) states that nasal decongestants should be used for periods not exceeding 10 to 15 days. One comment recommended that the warning be changed to limit use to no more than 10 days, and the other comments requested deletion of the warning entirely.

The agency disagrees with the comments. The comments have not submitted any data which prove that rebound congestion does not appear until after more than 7 days of use. Furthermore, individuals may respond differently to nasal congestion (Ref. 2). An individual's psychological state can affect the occurrence and degree of rebound congestion (Ref. 3 and 4).

The Panel reviewed several references (Refs. 3, 5, and 6) which provided a basis for the 3-day warning. Messek (Ref. 5) reported the occurrence of rebound congestion 90 to 120 minutes after the use of a nasal decongestant. Another nasal decongestant produced rebound congestion 6 hours after use. Rudiger (Ref. 3) reported rebound congestion approximately 4 hours after use. Biesalski (Ref. 6) found that a nasal decongestant caused rebound congestion after 5 hours. These data show that nasal decongestants can produce rebound congestion after a short period of use. Therefore, it cannot be categorically stated that rebound congestion does not begin to appear until more than 7 days after starting use of a nasal decongestant as one comment contended.

The Panel recognized that "because of the remarkable degree of nasal decongestion which follows topical application of these agents, there is a tendency on the part of patients to administer nasal decongestants too frequently and for too long a period of time." Prolonged use of topical nasal decongestants may be accompanied by a rebound phenomenon in which the initial vasoconstriction is followed by vasodilation and congestion. Thus, continued use can intensify nasal congestion. Because of the nasal congestion caused by the rebound effect, there is a tendency for an individual to habitually use a nasal decongestant. Therefore, the Panel concluded that a warning to discourage use beyond several days is necessary. The Panel reviewed references concerning persistent nasal congestion caused by the habitual use of nasal decongestants for varying periods of time, ranging from 6 to 23 months (Refs. 7 and 8). Because of the Panel's concern about the problem of rebound congestion leading to prolonged usage of nasal decongestants, it recommended a 3-day limitation on the use of these products. In addition, in order to further curb the continuous use of topical nasal decongestants, the Panel recommended that a physician be seen if symptoms persist for more than 3 days.

The agency concludes that the 3-day warning is justified in view of the above discussion. Therefore, the 3-day warning in § 341.80(b)(1)(ii) (redesignated as § 341.80(c)(2) (iii)(*a*) and (vi)) is appropriate for topical nasal decongestants except 1-desoxyephedrine which has a 7-day limit (see comment 8 above.) In addition, the agency has revised the format of the "Warnings" section in § 341.80(b) (redesignated as § 341.80(c) is this tentative final monograph) for clarity and to conform to the format of recently published monographs.

References

(1) "AMA Drug Evaluations," 2d Ed., Publishing Sciences Group, Acton, MA, p. 469, 1973.

(2) Harris, H.H., "Comparative Study of Decongestive Effectiveness of Oxymetazoline Hydrochloride in Rhinitis," *EENT Digest*, 46:41–43, 1967.

(3) Rudiger, W., "Investigations of the passability of air through the nose under the effect of a new vasoconstricting agent," (English translation), ("Ensaios sobre a permeabilidade nasal ao ar com o emprego de nova substancia vasoconstritora"), *HNO Wegweiser*, 7:77–80, 1958.

(4) Connell, J.T., "Effectiveness of Topical Nasal Decongestants," *Annals of Allergy*, 27:541–546, 1969.

(5) Messek, H., "The Effect of Different Vasoconstrictors on Various Qualities of the Nasal Mucosa," (English translation), ("Die Wirkung verschiedener Vasokonstriktoria auf einige Qualitaten der Nasenschleimhaut"), *Monatsschrift fur Ohrenheilkunde und Laryngo-Rhinologie, 96:294–306, 1962.*

(6) Biesalski, P., and K. Marquardt, "Treatment of Rhinitis of Early Childhood. Thermoelectric Studies on Decongestant Nasal Drugs," (English translation), "Zur Behandlung der Rhinitis im fruhen Kindesalter. Thermoelektrische Untersuchungen an abschwellender Nasenmitteln"), *Schweizerische Medizinische Wochenschrift,*, 89:510–512,1959.

(7) Putnam, L.E., and R.P. Herwick, "Privine Dependence of Two Years Duration," *Journal of the American Medical Association*, 130:702–703, 1946.

(8) Thomas, J.W., and U. Fabiano, "Privine Sensitivity: A Report of Eight Cases," *Southern Medical Journal*, 39:658–664, 1946.

25. One comment proposed that the Panel's recommended warning statement for topical nasal decongestants in § 341.80(b)(1)(i) "Do not exceed recommended dosage because symptoms may occur such as burning, stinging, sneezing, or increase of nasal discharge" be required only if the active ingredient is administered topically as a drop or spray directly to the nasal mucosa. The comment contended that requiring this warning for other dosage forms is unnecessary and is not supported by available data.

The agency disagrees with the comment's contention that this warning is unnecessary for dosage forms other than those administered topically as a drop or spray. Topical nasal decongestants may be administered as

drops, sprays, jellies, or inhaled vapors. The comment did not specify which other dosage forms should not be required to be labeled with the warning recommended by the Panel § 341.80(b)(1)(i); nor did the comment submit any data to show that this warning statement is unnecessary for other dosage forms of topical nasal decongestants.

The agency believes that this warning statement should apply to all topical nasal decongestant active ingredients administered as a drop, spray, jelly, or in an inhalant dosage form. Evaluation of the studies reviewed by Panel on propylhexedrine reveals that slight stinging occurred in some cases (41 FR 38402). Because nasal decongestants when used in all of these forms, i.e., drops, sprays, inhalants, and jellies, are administered to the nasal mucosa through the nostrils, the warning statement regarding burning, stinging, sneezing, or increase in nasal discharge is appropriate on these dosage forms. Therefore, the comment is not accepted. This warning, which has been revised to read: "Do not exceed recommended dosage because burning, stinging, sneezing, or increase of nasal discharge may occur," will be required for all dosage forms of topical nasal decongestants.

26. One comment suggested that the Panel's recommended warning statement for topical nasal decongestants in § 341.80(b)(1)(ii) "Do not use this product for more than 3 days. If symptoms persist, consult a physician," should apply only if the nasal decongestant is administered topically as a drop or spray. The comment also recommended that other forms to topical administration, such as via a "lozenge or mouthwash," should appropriately use the "7-day warning" recommended by the Panel for oral nasal decongestants in § 341.80(b)(2)(ii).

The agency agrees with the Panel that topical nasal decongestants administered as a drop or spray should not be used for more than 3 days because rebound congestion is likely to occur with prolonged use. Nasal decongestants in lozenges and mouthwashes are considered to be topical nasal decongestants; however, their route of administration is different from that of ingredients administered in a drop or spray. Lozenges and mouthwashes introduce the nasal decongestant through the oral cavity and the nasopharynx. Because of this difference in routes of administration, topical nasal decongestants in lozenges and mouthwashes are unlikely to cause rebound congestion. The Panel recommended the camphor, thymol, menthol/peppermint oil, and eucalyptol/eucalptus oil be used as topical nasal decongestants in lozenges and mouthwashes. The Panel's review of these active ingredients indicates that rebound congestion does not occur with these ingredients. The ingredients in the lozenges and mouthwashes are of a different pharmacologic group from those in topical nasal decongestants administered in drop or spray dosage forms. In view of this, it would be reasonable to conclude that use of the nasal decongestants recommended by the Panel for use in lozenges and mouthwashes for a longer period than 3 days would not result in rebound congestion.

The agency concludes that, although nasal decongestants in lozenges and mouthwashes are considered to be topically administered, the specific warning statement concerning 3-day use should not apply in the labeling of these specific topical nasal decongestants and agrees with the comment that it may be more appropriate to require the use of the "7-day warning" as stated in § 341.80(b)(2)(ii) (redesignated as § 341.80(c)(1)(*b*) in this document). The agency points out that none of the ingredients listed above are included in the tentative final monograph; hence, no revisions are currently needed in the Panel's recommended monograph.

27. One comment suggested that the Panel's recommended warning statement in § 341.80(b)(1)(iii) "The use of this dispenser by more than one person may spread infection" be required only for products administered by inhalers and not for nasal decongestants administered by other routes of administration.

The Panel pointed out that the use of a dispenser by more than one person may spread infection. The comment did not specify the other routes of administration of nasal decongestants. A nasal decongestant drug may also be administered by direct application into the nostrils in the form of a drop, spray, or nasal jelly. The use of a dropper, nasal spray, or nasal jelly applicator by more than one person may also result in the spread of infection. Therefore, the agency disagrees with the comment's recommendation that the warning should be required for inhalant nasal decongestants only and concludes that this warning statement should be required in the labeling for all topical nasal decongestant products which are directly applied to the nasal mucosa or directly inhaled through the nostrils. The agency has slightly revised the Panel's warning to make it more readily understood by consumers. The warning in § 341.80(c)(2)(i)(*b*) in this tentative final monograph reads as follows: "The use of this container by more than one person may spread infection."

28. One comment stated that the Panel's recommended labeling for xylometazoline hydrochloride contains special warnings related to the use of adult and pediatric concentrations of the drug, while no special warnings are suggested for the different concentrations of oxymetazoline hydrochloride. The comment argued that the labeling requirements for similar ingredients should be standard and requested that the additional warning statements be removed from the labeling for xylometazoline hydrochloride.

The comment refers to the warning recommended by the Panel in § 341.80(b)(10) for 0.05 percent zylometazoline hydrochloride which states, "Do not give this product to children under 2 years except under the advice and supervision of a physician," and the warning in § 341.80(b)(11) for 0.1 percent xylometazoline hydrochloride which states, "For adult use only. Do not give this product to children under 12 years except under the advice and supervision of a physician." The comment argued that similar warnings were not recommended by the Panel for oxymetazoline hydrochloride.

The agency has reviewed the literature for oxymetazoline hydrochloride and xylometazoline hydrochloride used as topical nasal decongestants. Oxymetazoline hydrochloride and xylometazoline hydrochloride are vasoconstrictors which may cause side effects. They also have a longer duration of action than the other Category I topical nasal decongestants. In a small child it is difficult to measure a correct dose and the child may inadvertently receive an excessive dose by swallowing the administered medication. Because these drugs are potent, long-acting, and the possibility of systemic effects exists, the agency believes that, in the interest of safety, oxymetazoline hydrochloride and xylometazoline hydrochloride should not be used in children under 6 years of age unless directed by a doctor. Therefore, the agency is restricting the use of both xylometazoline and oxymetazoline in children under 6 years of age. The agency is proposing that labeling for the use of oxymetazoline hydrochloride and xylometazoline hydrochloride in children under 6 years of age be provided to health professionals, but not to the general public. Thus, the Panel's recommended dosage instructions for oxymetazoline

hydrochloride and xylometazoline hydrochloride for children under 6 years of age in § 341.20 (c) and (h) have been deleted and moved to professional labeling in § 341.90 (m) and (n). The Panel's recommended warnings in § 341.80 (b) (3)(ii), (4), (5), first part of (6), and (7) through (11), have been revised in order to conform to the format of recently published tentative final monographs. These warnings have been moved from § 341.80(b) and included as directions in new § 341.80(d). Therefore, although the agency is deleting the warning regarding children's dosages for 0.05 percent xylometazoline from general OTC labeling, the directions for 0.05 percent oxymetazoline and 0.05 percent xylometazoline will state that the product is for use by adults and children 6 to under 12 years of age and that for use in children under 6 years of age a doctor should be consulted.

Regarding the comment's request for deletion of the Panel's recommended warning in § 341.80(b)(11) dealing with the 0.01-percent concentration of xylometazoline, the agency concludes that, based on the Panel's recommended concentrations, which the agency has adopted in this tenative final monograph, there is a need for a statement on products containing 0.1 percent xylometazoline against use by children under 12 years of age (because the 0.05 percent concentration is to be used in this age group). Thus, although the warning in § 341.80(b)(11) has been removed from the warnings section, as noted above, the content of the warning has been retained and restated as directions in new § 341.80(d)(2)(vii) (*a*)(*1*) and (*b*)(*1*). There is, however, no need for such a statement on products containing oxymetazoline because the same strength solution (0.05 percent) is used for both adults and children 6 to under 12 years of age; there is no 0.1 percent concentration of oxymetazoline proposed for inclusion in the monograph.

29. One comment was opposed to the Panel's recommended warning for inhalant nasal decongestant products in § 341.80(b)(3)(v): "*Caution:* Not for use by mouth." The comment stated that use by mouth is not a normal or expected use of this dosage form and that the directions for use clearly indicate that the product is to be used intranasally. The comment further stated that the company's records show no evidence of inadvertent misuse in this way due to lack of understanding. The comment believed that this warning, rather than providing needed instruction, actually has a potential for inciting possible abuse by stimulating the imagination. The comment recommended that this warning not be required for inhalers.

The agency agrees with the comment's recommendation that the warning in § 341.80(b)(3)(iv), "*Caution:* Not for use by mouth" is not needed for inhalant nasal decongestants. The dosage and directions for propylhexedrine in § 341.80(d)(2)(vi) and the dosage and directions for l-desoxyephedrine in § 341.80(d)(2)(i) of this tentative final monograph clearly indicate that these inhalants are to be used intranasally. Therefore, the warning recommended by the Panel in § 341.80(b)(3)(iv) for inhalant nasal decongestants will not be included in this tentative final monograph.

30. One comment recommended that the "warning" proposed by the Panel in § 341.80(b)(3)(i) concerning warming nasal decongestant inhalers before use should be deleted or moved to the "Directions" section. The comment expressed the opinion that, based on its extensive consumer experience with inhaler products, this instruction is unnecessary.

The agency agrees that the Panel's recommended warning in § 341.80(b)(3)(i), "This inhaler should be warmed in the hand before use to increase effectiveness," should be deleted. Inhalers are designed to release a safe and effective dose of active drug through vaporization at room temperature. The agency has reviewed the Panel's report, and additional material (Refs. 1, 2, and 3), and can find no scientific or medical data to support the inclusion of this instruction in the monograph. Therefore, the agency has deleted this instruction from § 341.80(b)(3) of the Panel's recommendations.

References

(1) Harvey, S.C., "Sympathomimetic Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, p. 820, 1975.

(2) Kennon, L., and J.J. Gulesich, "Some Aspects of Inhaler Technology," *Journal of Pharmaceutical Sciences*, 51:278–286, 1972.

(3) Ziment, I., "Respiratory Pharmacology and Therapeutics," W.B. Saunders Co., Philadelphia, p. 327, 1978.

F. Comments on Testing Guidelines

31. Two comments disagreed with the Panel's recommendation that smoking by test subjects should be prohibited 24 hours prior to and during the testing of nasal decongestant drugs. They argued that coryza and hay fever studies have shown that smokers constitute the majority of the target population and that it is therefore practical to attempt to determine the response of smokers to nasal decongestants. The comments also contented that this recommendation would make it more difficult to find suitable test subjects and that studies might become prohibitive in both cost and time. Another potential problem cited in the comments was the possibility that both the psychological effects of smoking withdrawal, e.g., tension and anxiety, as well as the decongestant effect of nasal decongestant drugs might modify the automatic nervous system enough during testing to result in result in studies with biased conclusions. Clinical data and a statistical analysis, which alleged that smoking has no discernible consistent effect on results obtained from testing nasal decongestants, were submitted as part of one of the comments (Ref. 1).

The agency has reviewed the results of these studies. They showed that the effect of the various drugs on the nasal flow rate as well as the clinical symptoms of both hay fever and acute coryza on smokers were frequently quite different from those observed in nonsmokers. The values sometimes differed tenfold, and the direction of the differences was unpredictable. These studies and the statistical analysis indicated that it would be advisable to use both smokers and nonsmokers in clinical trials for nasal decongestants.

The agency reviewed another study on the response of over 500 subjects to nasal decongestants (Ref. 2). The test population included 43 percent smokers. No discernible difference in nasal airway resistence or in subjective assessment of congestion existed when the subjects entered the study. The results of the study showed that the smokers' response to every one of the topical nasal decongestants tested tended to be less than that of the nonsmokers; however, that difference was great enough to be significant in only one group (phenylephrine). The results of this study support the proposal that there should be no curtailment of smoking by subjects participating in nasal decongestant studies. Considering that a significant portion of the target population is made up of smokers, it seems advisable to use both smokers and nonsmokers in clinical trials. Based on the data reviewed, the agency disagrees with the Panel's recommendation that smokers be required to obstain from smoking 24 hours prior to and during participation in the testing of nasal decongestants. An important problem in studying smokers who have abstained from cigarettes for 24 hours is the introduction of anxiety, restlessness, and autonomic responses, which may influence their nasal resistence. As an alternative to the Panel's recommendation, the agency concludes that the results of testing in smokers and nonsmokers should be tabulated separately, analyzed separately, and submitted in this form

by the manufacturer. This procedure would permit analysis of the data to establish if smokers are indeed different from nonsmokers in their response to nasal decongestants.

(**Note.**—In revising the OTC drug review procedures relating to Category III, published in the **Federal Register** of September 29, 1981 (46 FR 47730), the agency advised that tentative final and final monographs will not include recomended testing guidelines for conditions that industry wishes to upgrade to monograph status. Instead, the agency will meet with industry representatives at their request to discuss testing protocols. The revised procedures also state the time in which test data must be submitted for consideration in developing the final monograph. (See also part II. paragraph A.2 below—Testing of Category II and Category III conditions.))

References

(1) Comment No. C0097, Docket No. 76N-0052, Dockets Management Branch.

(2) Hamilton, L.H., "Report on Response to Nasal Decongestants by Smokers and Nonsmokers," draft of unpublished paper in OTC Volume 040298.

32. One comment contended that the method of substantiating the claim "reduction of sinus pressure" for nasal decongestants, as described in the Panel's report at 41 FR 38414 and 38415, was a pilot approach, not widely used or recognized as a clinical research tool applicable to the documentation of sinus pressure changes, and could not be properly or reproducibly executed. This method involves the insertion of a trocar or needle into the maxillary sinus under topical anesthesia. The comment pointed out that the very act of repeatedly inserting the trocar or needle causes changes in the sinus pressure which makes this method impractical as a tool to substantiate pressure changes due to the nasal decongestant. In addition, the comment opposed the use of this method on moral and ethical grounds because it involved the use of "invasive surgical techniques" in volunteer subjects to obtain clinical research data on OTC drugs and therefore would not receive approval from institutional peer review committees.

The agency agrees with the comment. Further, the agency has determined that the claim "relieves sinus pressure" will be reclassified from Category III to Category I. (See comment 24 above.) Therefore, a discussion of methods to substantiate this claim is unnecessary.

II. The Agency's Tentative Adoption of the Panel's Report

A. Summary of Ingredient Categories and Testing of Category II and Category III Conditions

1. *Summary of ingredient categories.* The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and is proposing to reclassify one nasal decongestant active ingredient from Category III to Category I. For the convenience of the reader, the following table is included as a summary of the categorization of nasal decongestant active ingredients by the Panel and the proposed classification by the agency.

Nasal decongestant active ingredients	Panel	Agency
Beechwood creosote (oral)	III	III
Bornyl acetate (topical)	III	III
Camphor (topical/inhalant)	III	III
Cedar leaf oil (topical)	III	III
1-Desoxyephedrine (inhalant)	III	I
Ephedrine (oral)	III	III
Ephedrine hydrochloride (oral)	III	III
Ephedrine sulfate (oral)	III	III
Racephedrine hydrochloride (oral)	III	III
Ephedrine (topical)	I	I
Ephedrine hydrochloride (topical)	I	I
Ephedrine sulfate (topical)	I	I
Racephedrine hydrochloride (topical)	I	I
Eucalyptol/eucalyptus oil (topical/inhalant)	III	III
Menthol/peppermint oil (topical/inhalant)	III	III
Mustard oil (allylisothiocyanate) (topical/inhalant)	II	II
Naphazoline hydrochloride (topical)	I	I
Oxymetazoline hydrochloride (topical)	I	I
Phenylephrine hydrochloride (oral)	I	I
Phenylephrine hydrochloride (topical)	I	I
Phenylpropanolamine bitartrate (oral)	I	(1)
Phenylpropanolamine hydrochloride (oral)	I	(1)
Phenylpropanolamine maleate (oral)	I	(1)
Phenylpropanolamine hydrochloride (topical)	III	(1)
Propylhexedrine (inhalant)	I	I
Pseudoephedrine hydrochloride (oral)	I	I
Pseudoephedrine sulfate (oral)	I	I
Thenyldiamine hydrochloride (topical)	III	III
Thymol (inhalant)	III	III
Turpentine oil (spirits of turpentine) (oral)	II	II
Turpentine oil (spirits of turpentine) (topical/inhalant)	III	III
Xylometazoline hydrochloride (topical)	I	I

[1] To be addressed in a future FEDERAL REGISTER document.

2. *Testing of Category II and Category III Conditions.* The Panel recommended testing guidelines for nasal decongestant drug products (41 FR 38376 and 38437). The agency is offering these guidelines as the Panel's recomendations without adopting them or making any formal comment on them. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any nasal decongestant ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the **Federal Register** of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). This policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Changes

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the nasal decongestant section of the Panel's report and recommended monograph with the changes described in FDA's responses to the comments above and with other changes described in the summary below. A summary of the changes made by the agency follows.

1. The agency is amending the definitions proposed by the Panel in § 341.3 to include a definition of an "oral nasal decongestant drug" and a "topical nasal decongestant drug."

2. The agency is reclassifying 1-desoxyephedrine as a topical nasal decongestant (administered by a nasal inhaler) from Category III to Category I. Accordingly, this ingredient is included in the tentative final monograph in § 341.20(b)(1). In additon to the required labeling for all topical nasal decongestants, specific labeling requirements for 1-desoxyephedrine is being added in § 341.80(c)(2)(ii), and § 341.80(d)(2) (i) and (viii). (See comment 8 above.)

3. The agency is deleting the dosage instructions for the use of oxymetazoline hydrochloride and xylometazoline hydrochloride in children under 6 years of age that were recommended by the Panel in § 341.20 (c) and (h) and moving these dosage instructions to professional labeling in § 341.90 (m) and (n). The agency concluded that oxymetazoline hydrochloride and xylometazoline hydrochloride should not be used in children under 6 years of age unless directed by a doctor. (See comment 28 above.)

4. The agency is amending the dosage instruction for oxymetazoline hydrochloride that was recommended by the Panel in § 341.20(c) (redesignated as § 341.80(d)(2)(iv) so that the dosage interval of use will be stated in terms of "hours" as follows: "Adults and children 6 to under 12 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 10 to 12 hours. Do not exceed 2 applications in any 24-hour period. Children under 6 years of age: consult a doctor." The Panel had recommended a topical dosage of oxymetazoline hydrochloride of "2 to 3 drops or sprays of a 0.05-percent aqueous solution in each nostril 2 times daily (in the morning and evening)." The recommended dosages for all of the other topical nasal decongestants in the Panel's monograph were stated in terms of "hours." The agency has evaluated data on the use of this drug and concludes that a dosage interval of

every 10 to 12 hours is an appropriate interval for this drug (Ref. 1).

Reference

(1) Mujik, M., and J.M. Van Rossum, "Comparative Pharmacodynamics of Sympathomimetic Imidazolines: Studies on Intestinal Smooth Muscle of the Rabbit and the Cardivascular System of the Cat," *Archives Internationales de Pharamacodynamie et de Therapie*, 155:432–449, 1965.

5. The agency is classifying 1 percent phenylephrine hydrochloride as a Category I topical nasal decongestant. Because the data suggest that the 1-percent concentration is more likely to induce rebound congestion, the agency is proposing the following warning in § 341.80(c)(v) for the 1-percent concentration of phenylephrine hydrochloride: "Frequent use of this product may cause nasal congestion to recur or worsen." (See comment 17 above.)

6. The agency is deleting from the Panel's recommendation in § 341.20(d)(2) the provision that topical nasal decongestant drug products containing phenylephrine hydrochloride when administered to children 2 to under 6 years of age should be used only in the form of nose drops and not in the form of nasal sprays. The dosage instruction for phenylephrine hydrochloride in a 0.125-percent aqueous solution idendified in § 341.80(d)(2)(v)(*a*)(*4*) in the tentative final monograph will now permit the use of drops or sprays for children 2 to under 6 years of age. (See comment 19 above.)

7. Phenylpropanolamine preparations for use as nasal decongestants are not classified in this tentative final monograph. Instead, issues related to the use of phenylpropanolamine in OTC nasal decongestant drug products, as well as in OTC weight control drug products, will be discussed in detail in a separate document to be published in the **Federal Register** in the near future.

8. The agency is deleting the statement regarding propylhexedrine proposed by the Panel in § 341.20(f): "This inhaler should retain effectiveness for a minimum of 2 to 3 months." A modification of that statement and a related statement are now included in new § 341.80(d)(2)(viii), "Other required statements," and are applicable to inhalers containing either 1-desoxyephedrine or propylhexedrine. The new statements are: "This inhaler is effective for a minimum of 3 months after first use," and "Keep inhaler tightly closed." The agency concluded that these statements are important for consumers' information because volatile substances such as 1-desoxyephedrine and propylhexedrine when used in an inhaler becomes less potent upon continued exposure to air. Manufacturers of these products recognize this fact and include such statements on their product labels (Ref. 1).

Reference

(1) Baker, C.E., et al., "Physicians' Desk Reference for Nonprescription Drugs," 3rd Ed., Medical Economics Co., Oradell, NJ, pp. 582, 583, and 659, 1982.

9. The agency is modifying the Panel's recommendations in § 341.20(g) (redesignated as § 341.80(d)(1)(ii)) by providing for a more flexible dosage interval and by reducing the adult oral dosage of pseudoephedrine preparations from 60 mg every 4 hours, not to exceed 360 mg in 24 hours, to 60 mg every 4 to 6 hours not to exceed 240 mg in 24 hours. For children 6 to under 12 years of age, the oral dosage has been reduced from 30 mg every 4 hours, not to exceed 180 mg in 24 hours, to 30 mg every 4 to 6 hours, not to exceed 120 mg in 24 hours. For children 2 to under 6 years of age, the oral dosage has been reduced from 15 mg every 4 hours, not to exceed 90 mg in 24 hours, to 15 mg every 4 to 6 hours, not to exceed 60 mg in 24 hours. (See comment 18 above.)

10. The agency is adding to § 341.80 a "Statement of identity" paragraph (designated as § 341.80(a)) to conform with the format of other recently published advance notices of proposed rulemaking or tentative final monographs. Inclusion of the new paragraph has necessitated a redesignation of § 341.80(a) to § 341.80(b), and § 341.80(b) to § 341.80(c). The agency is also redesignating Subpart D as Subpart C and placing the labeling sections of the monograph in Subpart C.

11. The agency is combining several indications that were required under § 341.80(a) (redesignated as § 341.80(b)). The agency believes that combining these indications presents them to the consumer in a clearer and more concise manner. Therefore, the indications recommended by the Panel in § 341.80(a) (1), (2), and (3) have been revised, combined, and redesignated as § 341.80(b)(1). The Panel's recommended indications in § 341.80(a) (5), (6), and (8) are also being combined, revised, and redesignated as new § 341.80(b)(2) ("Other allowable indications") which provides manufacturers the option to use additional indications in labeling.

12. The agency is reclassifying the claim "relieves sinus pressure" from Category III to Category I. Accordingly, the Category I indications for nasal decongestants recommended by the Panel in § 341.80(a) (9) and (10) (redesignated as § 341.80(b)(2) (iv) and (v)) are being expanded to include this claim in the tentative final monograph as follows:

"(iv) 'Helps decongest sinus openings and passages; relieves sinus pressure.'"

"(v) 'Promotes nasal and/or sinus drainage; relieves sinus pressure.'" (See comment 23 above.)

13. The agency is deleting the Panel's recommendation in § 341.80(a)(11) that claims relating to duration of effect for nasal decongestant products must be substantiated and accompanied by a specific time period. The agency points out that duration of effect has been included in the established dosages and directions for these products by stating the frequency of use (in terms of hours), which indirectly tells the consumer the duration of the products' effects.

14. The agency is deleting the Panel's recommendation for topical nasal decongestants in § 341.80(a)(12) regarding statements related to time to onset of action, such as fast or quick. As with all OTC drug products, nasal decongestants are expected to achieve their intended results within a reasonable period of time. However, the specific period of time within which nasal decongestants achieve these results is not related in a significant way to the safe and effective use of the products. Therefore, terms such as "fast" or "quick" are outside the scope of the OTC drug review. For other classes of products in the OTC drug review, however, statements relating to time of action may properly fall within the list of terms covered by the monograph. (See comment 2 above.)

15. The agency is deleting the Panel's recommendation in § 341.80(a)(13) which refers to claims describing a "cooling sensation" demonstrated by certain topical nasal decongestants. The agency has concluded that it has no objection to the use of terms which describe certain physical and chemical qualities of a drug, as long as these terms do not imply that any therapeutic effect might occur, are true and not misleading, and are distinctly separated from labeling indications. Terms describing product characteristics, e.g., color, odor, flavor, and feel, appear in the labeling for consumers' information and will not be specifically addressed in the monograph.

16. The agency is revising the warnings section proposed by the Panel in § 341.80(b) (redesignated as § 341.80(c)) for clarity by listing the warnings according to ingredient and dosage form (i.e., oral or topical nasal decongestants).

17. The agency is revising the warning recommended by the Panel in § 341.80(b)(1)(i) (redesignated as § 341.80(c)(2)(i)(*a*)) to read as follows: "Do not exceed recommended dosage

because burning, stinging, sneezing, or increase of nasal discharge may occur." (See comment 25 above.)

18. The agency is slightly revising the warning recommended by the Panel in § 341.80(b)(1)(iii) (redesignated as § 341.80(c)(2)(i)(*b*)) to read as follows: "The use of this container by more than one person may spread infection." (See comment 27 above.)

19. The agency is deleting the word "high" (in reference to fever) from the warning for oral nasal decongestants recommended by the Panel in § 341.80(b)(2)(ii) (redesignated as § 341.80(c)(1)(i)(*b*)). Fever can be defined as a body temperature above the normal temperature of 98.6 °F (37 °C). In the same or different disease states, however, fevers may vary significantly. Fever may be low grade, moderate, high, intermittent, or sustained. The particular characteristics of a fever depend on the disease state, and, in many cases, on the stage of development of the disease. The word "high" has been deleted from the warning because the agency believes that it is important for the consumer to recognize the presence of fever, regardless of whether the fever is high or low. Additionally, the Panel's warning in § 341.80(6)(2)(ii) (redesignated as § 341.80(c)(1)(i)(*b*)) is being revised to conform with the format of similar warnings in the tentative final monograph.

20. The agency is amending the warning for oral nasal decongestants recommended by the Panel in § 341.80(b)(2)(iii) (redesignated as § 341.80(c)(1)(i)(*c*)), to include "difficulty in urination." The amended warning will read as follows: "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor." (See comment 13 above.) In addition, the agency has concluded that the warning in new § 341.80(c)(1)(i)(*c*)) for oral nasal decongestants should also apply to all topical nasal decongestants, except topical inhalants. Accordingly, the warning is also being added to this tentative final monograph as § 341.80(c)(2)(iii)(*b*). (See comment 4 above.) (NOTE: For oral and topical nasal decongestant warnings in the monograph, the agency is proposing to use the word "use" to denote topical use, and the word "take" to denote oral use.)

21. The agency is simplifying the warning recommended by the Panel in § 341.80(b)(2)(iv) (redesignated as § 341.80(c)(1)(i)(*d*)) to read as follows: "*Drug interaction precaution.* Do not take this product if you are presently taking a prescription drug for high blood pressure or depression, without first consulting your doctor." (See comment 22 above.)

22. The agency is deleting the warning recommended by the Panel in § 341.80(b)(3)(i) which states: "This inhaler should be warmed in the hand before use to increase effectiveness." The agency found this warning unnecessary because inhalers are designed to release a safe and effective dose of active drug through vaporization at room temperature. (See comment 30 above.)

23. The agency is moving and revising the Panel's recommended warnings in § 341.80(b) (3)(ii), (4), (5), first part of (6), (7), (8), (9) (10), and (11) and including them as part of the directions in the appropriate sections in new § 341.80(d).

24. The agency is moving the warning recommended by the Panel in § 341.80(b)(3)(iii) and is including it as part of the directions. The warning previously stated: "Children should not have unsupervised access to this inhaler." The agency believes that a statement of this should apply not only to inhalers, but also to any topical nasal decongestant product labeled for use in children because of the possibility of adverse reactions occurring from misuse or overuse of these products. Therefore, the phrase "with adult supervision" is being added to the directions for topical nasal decongestants which are labeled for use in children.

25. The agency is deleting the Panel's recommended warning in § 341.80(b)(3)(iv) for inhalant nasal decongestants which states: "*Caution:* Not for use by mouth." The agency has concluded that the directions for use of inhalant nasal decongestants as stated in § 342.80(d)(2) (i) and (vi) in the tentative final monograph clearly indicate that these products are to be used intranasally and not by mouth. (See comment 29 above.)

26. The agency is revising for clarity the warning for 0.05 percent naphazoline hydrochloride recommended by the Panel in § 341.80(b)(6) (redesignated as § 341.80(c)(2)(iv)) to read as follows: "Do not use this product in children under 12 years of age because it may cause sedation if swallowed." (See comment 14 above.)

27. The agency is adding to § 341.80 a "*Directions*" paragraph (designated as § 341.80(d)), to conform with the format of other recently published advance notices of proposed rulemaking and tentative final monographs. To simplify and clarify the labeling, FDA is also slightly modifying the Panel's directions for use.

28. The Panel did not address topical nasal decongestants in a jelly dosage form, although these products are presently marketed. The agency has concluded that a nasal jelly should not be used in children under 6 years of age and therefore this restriction is being added to the appropriate "Directions" sections. (See comment 19 above.)

29. The warning concerning enlargement of the prostate gland in § 341.80(c)(1)(i)(*c*) and § 341.80(c)(2)(iii)(*b*) proposed by the agency in this document for oral and topical nasal decongestants is being modified for products labeled for use only in children. The reference to "enlargement of the prostate gland "is not needed for products labeled for use only in children. The new warning "Do not give this product to children who have heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor," is being added to the tentative final monograph in § 341.80(c)(1)(ii)(*c*) and § 341.80(c)(2)(ix)(*b*). (See comments 13 and 21 above.) Additionally, all warnings for products which are labeled for use only in children 2 to under 12 years of age are being designated in the monograph and reworded to reflect the administration of the products by adults rather than self administration. Warnings for products which are labeled for both adults and children are also being proposed in the tentative final monograph.

30. In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs to substitute the word "doctor" for "physician" in OTC drug monographs on the basis that the word "doctor" is more commonly used and better understood by consumers. Based on comments received to these proposals, the agency has determined that final monographs and any applicable OTC drug regulations will give manufacturers the option of using either the word "physician" or the word "doctor." This tentative final monograph proposes that option.

The agency proposes to revoke the existing warning and caution statements in § 369.20 for "nasal preparations; oil base," "nasal preparations in plastic spray containers," "nasal preparations; vasoconstrictors," and "phenylephrine hydrochloride preparations, oral" at the time that this monograph becomes effective.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the

Federal Register of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that not one of these rules, including this proposed rule for OTC nasal decongestant drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act, Pub. L. 96–354. That assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC nasal decongestant drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC nasal decongestant drug products. Types of impact may include, but are limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC nasal decongestant drug products should be accompanied by appropriate documentation. Because the agency has not previously invited specific comment on the economic impact of the OTC drug review on nasal decongestant drug products, a period of 120 days from the date of publication of this proposed rulemaking in the **Federal Register** will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has carefully considered the potential environmental effects of this proposal and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement therefore will not be prepared. The agency's finding of no significant impact, and the evidence supporting this finding, is contained in an environmental assessment (under 21 CFR 25.31, proposed in the **Federal Register** of December 11, 1979; 44 FR 71741), which may be seen in the Dockets Management Branch, Food and Drug Administration.

List of Subjects in 21 CFR Part 341

OTC drugs: Anticholinergics; Expectorants; Bronchodilators; Antitussives; Nasal decongestants.

On July 9, 1982 at 47 FR 40002, FDA proposed to amend 21 CFR Subchapter B by adding a new Part 341. Proposed Part 341, as amended on October 26, 1982 (47 FR 47520) and October 13, 1983 (48 FR 48576), would be further amended as follows:

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 it is proposed to make the following amendments:

PART 341—[AMENDED]

1. In proposed Subpart A, § 341.3 is amended by adding new paragraphs (h) and (i) to read as follows:

§ 341.3 Definitions.

* * * * *

(h) *Oral nasal decongestant drug.* A drug which is taken by mouth and acts systemically to reduce nasal congestion caused by acute or chronic rhinitis.

(i) *Topical nasal decongestant drug.* A drug which when applied topically inside the nose, in the form of drops, jellies, or sprays, or when inhaled intranasally reduces nasal congestion caused by acute or chronic rhinitis.

2. In Subpart B, new § 341.20 is added, to read as follows:

§ 341.20 Nasal decongestant active ingredients.

The active ingredients of the product consist of any of the following when used within the dosage limits and in the dosage forms established for each ingredient in § 341.80(d):

(a) *Oral nasal decongestants.* (1) Phenylephrine hydrochloride.

(2) Pseudoephedrine hydrochloride.

(3) Pseudoephedrine sulfate.

(b) *Topical nasal decongestants.* (1) 1-Desoxyephedrine.

(2) Ephedrine.

(3) Ephedrine hydrochloride.

(4) Ephedrine sulfate.

(5) Racephedrine hydrochloride.

(6) Naphazoline hydrochloride.

(7) Oxymetazoline hydrochloride.

(8) Phenylephrine hydrochloride.

(9) Propylhexedrine.

(10) Xylometazoline hydrochloride.

3. In proposed Subpart C, new § 341.80 is added and § 341.90 is amended by adding new paragraphs (m) and (n) to read as follows:

§ 341.80 Labeling of nasal decongestant drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "nasal decongestant."

(b) *Indications.* (1) The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the following phrase: "For the temporary relief of nasal congestion due to the common cold (cold), hay fever" (which may be followed by any of the following: "(allergic rhinitis)," "or other upper respiratory allergies," or "or other upper respiratory allergies (allergic rhinitis,") "or associated with sinusitus."

(2) *Other allowable indications.* In addition to the required information identified in paragraph (b)(1) of this section, the labeling of the product may contain any of the following statements provided such statements are neither placed in direct conjunction with information required to appear in the labeling nor occupy labeling space with greater prominence or conspicousness than the required information.

(i) "For the temporary relief of" (select one of the following: "stuffy nose," "stopped up nose," "nasal stuffiness," or "clogged up nose.")

(ii) (Selected one of the following: "Reduces swelling of," "Decongests," or "Helps clear") "nasal passages; shrinks swollen membranes."

(iii) "Temporarily restores freer breathing through the nose."

(iv) "Helps decongest sinus openings and passages; relieves sinus pressure."

(v) "Promotes nasal and/or sinus drainage; relieves sinus pressure."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *Oral nasal decongestants*—(i) *For products containing phenylephrine hydrochloride, pseudoephedrine hydrochloride, or pseudoephedrine sulfate identified in § 341.20(a) (1), (2), and (3) when labeled for adults.* (a) "Do not exceed recommended dosage because at higher doses nervousness, dizziness, or sleeplessness may occur."

(b) "Do not take this product for more than 7 days. If symptoms do not improve or are accompained by fever, consult a doctor."

(c) "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

(d) "*Drug Interaction Precaution.* Do not take this product if you are presently taking a prescription drug for high blood pressure or depression, without first consulting your doctor."

(ii) *For products containing phenylephrine hydrochloride, pseudoephedrine hydrochloride, or pseudoephedrine sulfate identified in § 341.20(a) (1), (2), and (3) when labeled for children under 12 years of age.* (a) "Do not exceed recommended dosage because at higher doses nervousness, dizziness, or sleeplessness may occur."

(b) "Do not give this product to children for more than 7 days. If symptoms do not improve or are accompained by fever, consult a doctor."

(c) "Do not give this product to children who have heart disease, high blood pressure, thyroid disease, or diabetes, unless directed by a doctor."

(d) "*Drug Interaction Precaution.* Do not give this product to a child who is taking a prescription drug for high blood pressure or depression, without first consulting the child's doctor."

(iii) *For oral nasal decongestant products labeled for both adults and children under 12 years of age.* The labeling of the product contains the warnings identified in paragraph (c)(1)(i) of this section.

(2) *Topical nasal decongestants*—(i) *For products containing any topical nasal decongestant identified in § 341.20(b) when labeled for adults.* (a) "Do not exceed recommended dosage because burning, stinging, sneezing, or increase of nasal discharge may occur."

(b) "The use of this container by more than one person may spread infection."

(ii) *For products containing 1-desoxyephedrine identified in § 341.20(b)(1) when used in an inhalant dosage form and when labeled for adults.* "Do not use this product for more than 7 days. If symptoms persist, consult a doctor."

(iii) *For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine hydrochloride, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, or xylometazoline hydrochloride identified in § 341.20(b) (2), (3), (4), (5), (6), (7), (8), and (10) when used as nasal sprays, drops, or jellies and when labeled for adults.* (a) "Do not use this product for more than 3 days. If symptoms persist, consult a doctor."

(b) "Do not use this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

(iv) *For products containing naphazoline hydrochloride identified in § 341.20(b)(6) at a concentration of 0.05 percent.* "Do not use this product in children under 12 years of age because it may cause sedation if swallowed."

(v) *For products containing phenylephrine hydrochloride identified in § 341.20(b)(8) at a concentration of 1 percent.* "Frequent use of this product may cause nasal congestion to recur or worsen."

(vi) *For products containing propylhexedrine identified in § 341.20(b)(9) when used in an inhalant dosage form and when labeled for adults.* "Do not use this product for more than 3 days. If symptoms persist, consult a doctor."

(vii) *For products containing any topical nasal decongestant identified in § 341.20(b) when labeled for children under 12 years of age.* The labeling of the product contains the warnings identified in paragraph (c)(2)(i) of this section.

(viii) *For products containing 1-desoxyephedrine identified in § 341.20(b)(1) when used in an inhalant dosage form and when labeled for children under 12 years of age.* "Do not use this product for more than 7 days. If symptoms persist, consult a doctor."

(ix) *For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine hydrochloride, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, or xylometazoline hydrochloride identified in § 341.20(b) (2), (3), (4), (5), (6), (7), (8), and (10) when used as nasal sprays, drops, or jellies, and when labeled for children under 12 years of age.* (a) "Do not use this product for more than 3 days. If symptoms persist, consult a doctor."

(b) "Do not use this product in children who have heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor."

(x) *For products containing propylhexedrine identified in § 341.20(b)(9) when used in an inhalant dosage form and when labeled for children under 12 years of age.* "Do not use this product for more than 3 days. If symptoms persist, consult a doctor."

(xi) *For topical nasal decongestant products labeled for both adults and for children under 12 years of age.* The labeling of the product contains the applicable warnings identified in paragraphs (c)(2)(i), (ii), (iii), and (vi) of this section.

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions":

(1) *Oral nasal decongestants*—(i) *For products containing phenylephrine hydrochloride identified in § 341.20(a)(1).* Adults: 10 milligrams every 4 hours not to exceed 60 milligrams in 24 hours. Children 6 to under 12 years of age: 5 milligrams every 4 hours not to exceed 30 milligram in 24 hours. Children 2 to under 6 years of age: 2.5 milligrams every 4 hours not to exceed 15 milligrams in 24 hours. Children under 2 years of age: consult a doctor.

(ii) *For products containing pseudoephedrine hydrochloride or pseudoephedrine sulfate identified in § 341.20(a) (2) and (3).* Adults: 60 milligrams every 4 to 6 hours not to exceed 240 milligrams in 24 hours. Children 6 to under 12 years of age: 30 milligrams every 4 to 6 hours not to exceed 120 milligrams in 24 hours. Children 2 to under 6 years of age: 15 milligrams every 4 to 6 hours not to exceed 60 milligrams in 24 hours. Children under 2 years of age: consult a doctor.

(2) *Topical nasal decongestants*—(i) *For products containing 1-desoxyephedrine identified in § 341.20(b)(1) when used in an inhalant dosage form.* The product delivers in each 800 milliliters of air 0.04 to 0.150 milligrams of 1-desoxyephedrine. Adults: 2 inhalations in each nostril not more often than every 2 hours. Children 6 to under 12 yearas of age (with adult supervision): 1 inhalation in each nostril not more often than every 2 hours. Children under 6 years of age: consult a doctor.

(ii) For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, or racephedrine hydrochloride identified in § 341.20(b) (2), (3), (4), and (5)—(a) *Nasal drops or sprays—For a 0.5-percent aqueous solution.* Adults: 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Children 6 to under 12 years of age (with adult supervision): 1 or 2 drops or sprays in each nostril not more often than every 4 hours. Children under 6 years of age: consult a doctor.

(b) *Nasal jelly—For a 0.5-percent water-based jelly.* Adults and children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages not more often than every 4 hours. Children under 6 years of age: consult a doctor.

(iii) *For products containing naphazoline hydrochloride identified in § 341.20(b)(6)—(a) Nasal drops or sprays—(1) For a 0.05-percent aqueous solution.* Adults: 1 or 2 drops or sprays in each nostril not more often than every 6 hours. Do not give to children under 12 years of age unless directed by a doctor.

(2) For a 0.025-percent aqueous solution. Children 6 to under 12 years of age (with adult supervision): 1 or 2 drops or sprays in each nostril not more often than every 6 hours. Children under 6 years of age: consult a doctor.

(b) Nasal jelly—(1) For a 0.05 percent water-based jelly. Adults: place a small amount in each nostril and inhale well back into the nasal passages not more often than every 6 hours. Do not give to children under 12 years of age unless directed by a doctor.

(2) For a 0.025-percent water-based jelly. Children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages not more often than every 6 hours. Children under 6 years of age: consult a doctor.

(iv) *For products containing oxymetazoline hydrochloride identified in § 341.20(b)(7)—(a) Nasal drops or sprays—For a 0.05-percent aqueous solution.* Adults and children 6 to under 12 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 10 to 12 hours. Do not exceed 2 applications in any 24-hour period. Children under 6 years of age: consult a doctor.

(b) Nasal jelly—For a 0.05 percent water-based jelly. Adults and children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages not more often than every 10 to 12 hours. Do not exceed 2 applications in any 24-hour period. Children under 6 years of age: consult a doctor.

(v) *For products containing phenylephrine hydrochloride identified in § 341.20(b)(8)—(a) Nasal drops or sprays—(1) For a 1-percent aqueous solution.* Adults: 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Do not give to children under 12 years of age unless directed by a doctor.

(2) For a 0.5-percent aqueous solution. Adults: 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Do not give to children under 12 years of age unless directed by a doctor.

(3) For a 0.25-percent aqueous solution. Adults and children 6 to under 12 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Children under 6 years of age: consult a doctor.

(4) For a 0.125-percent aqueous solution. Children 2 to under 6 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Children under 2 years of age: consult a doctor.

(b) Nasal jelly—(1) For a 1-percent water-based jelly. Adults: place a small amount in each nostril and inhale well back into the nasal passages not more often than every 4 hours. Do not give to children under 12 years of age unless directed by a doctor.

(2) For a 0.5-percent water-based jelly. Adults: place a small amount in each nostril and inhale well back into the nasal passages not more often than every 4 hours. Do not give to children under 12 years of age unless directed by a doctor.

(3) For a 0.25-percent water-based jelly. Adults and children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages not more often than every 4 hours. Children under 6 years of age: consult a doctor.

(vi) *For products containing propylhexedrine identified in § 341.20(b)(9) when used in an inhalant dosage form.* The product delivers in each 800 milliliters of air 0.04 to 0.50 milligrams of propylhexedrine. Adults and children 6 to under 12 years of age (with adult supervision): 2 inhalations in each nostril not more often than every 2 hours. Children under 6 years of age: consult a doctor.

(vii) *For products containing xylometazoline hydrochloride identified in § 341.20(b)(10)—(a)* Nasal drops or sprays—*(1) For a 0.1-percent aqueous solution.* Adults: 2 or 3 drops or sprays in each nostril not more often than evey 8 to 10 hours. Do not give to children under 12 years of age unless directed by a doctor.

(2) For a 0.05-percent aqueous solution. Children 6 to under 12 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than evey 8 to 10 hours. Children under 6 years of age: consult a doctor.

(b) Nasal jelly—(1) For a 0.1-percent water-based jelly. Adults: placed a small amount in each nostril and inhale well back into the nasal passages not more often than every 8 to 10 hours. Do not give to children under 12 years of age unless directed by a doctor.

(2) For a 0.05-percent water-based jelly. Children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages not more oftern than evey 8 to 10 hours. Children under 6 years of age: consult a doctor.

(viii) *Other required statements—For products containing 1-desoxyephedrine or propylhexedrine identified in § 341.20(b)(1) or (9) when used in an inhalamt dosage form.*

(a) "This inhaler is effective for a minimum of 3 months after first use."

(b) "Keep inhaler tightly closed."

(c) The word "physician" may be substituted for the word "doctor" in any of the labeling statements above.

§ 341.90 Professional labeling.

* * * * *

(m) *For products containing oxymetazoline hydrochloride identified in § 341.20(b)(7).* Children 2 to under 6 years of age: 2 or 3 drops of sprays in each nostril of a 0.025-percent aqueous solution not more often than every 10 to 12 hours. Do not exceed 2 applications in any 24-hour period.

(n) *For products containing xylometazoline hydrochloride identified in § 341.20(b)(10).* Children 2 to under 6 years of age: 2 or 3 drops or sprays in each nostril of a 0.05-percent aqueous solution not more often than every 8 to 10 hours.

Interested persons, may, or or before May 15, 1985, submit to the Docket Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. The agency has provided this 120 day period (instead of the normal 60 days) because of the number of OTC drug review documents being published concurrently. Written comments on the agency's economic impact determination may be submitted on or before May 15, 1985. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the hearing of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register.**

Interested persons, on or before January 15, 1986, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before March 17, 1986. These dates are consistent with

the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addresed to the Dockets Management Branch (HFA-305) (address above). Received data and comments may also be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on March 17, 1986. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register** unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Dated: December 31, 1984.

Frank E. Young,

Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310, 341, and 369

[Docket No. 76N–052N]

RIN 0905–AA06

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Final Monograph for OTC Nasal Decongestant Drug Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing conditions under which over-the-counter (OTC) nasal decongestant drug products (drug products used to relieve nasal congestion caused by acute or chronic rhinitis) are generally recognized as safe and effective and not misbranded. FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and all new data and information on nasal decongestant drug products that have come to the agency's attention. Also, this final rule amends the regulation that lists nonmonograph active ingredients by adding those OTC nasal decongestant ingredients that have been found to be not generally recognized as safe and effective and that were not previously listed in the regulation. This final monograph is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: August 23, 1995.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD–810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of September 9, 1976 (41 FR 38312), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products, together with the recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (Cough-Cold Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in these drug classes. Interested persons were invited to submit comments by December 8, 1976. Reply comments in response to comments filed in the initial comment period could be submitted by January 7, 1977.

In accordance with § 330.10(a)(10), the data and information considered by the Cough-Cold Panel were put on display in the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857, after deletion of a small amount of trade secret information.

The agency's proposed regulations, in the form of tentative final monographs, for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products were issued in the following segments: Anticholinergics and expectorants, bronchodilators, antitussives, nasal decongestants, antihistamines, and combinations. The fourth segment, the tentative final monograph for OTC nasal decongestant drug products, was published in the **Federal Register** of January 15, 1985 (50 FR 2220). Interested persons were invited to file by May 15, 1985, written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal. Interested persons were invited to file comments on the agency's economic impact determination by May 15, 1985. New data could have been submitted until January 15, 1986, and comments on the new data until March 17, 1986.

In the **Federal Register** of June 19, 1992 (57 FR 27658), FDA published a notice of proposed rulemaking to amend the tentative final monograph for OTC nasal decongestant drug products to modify the drug interaction precaution statement as follows:

Drug interaction precaution. Do not take this product if you are taking a prescription drug containing a monoamine oxidase inhibitor (MAOI) (certain drugs for depression or psychiatric or emotional conditions), without first consulting your doctor. If you are uncertain whether your prescription drug contains an MAOI, consult a health professional before taking this product.

In the **Federal Register** of July 30, 1992 (57 FR 33663), FDA published a correction to change the wording of the first sentence of the statement from, "Do not take * * *" to "Do not use * * *." In the **Federal Register** of August 6, 1992 (57 FR 34734), the agency extended the comment period to October 5, 1992, to obtain additional comments on whether the drug interaction precaution statement should be expanded to include MAO B drugs, such as selegiline. The agency asked whether the proposed drug interaction precaution statement should be expanded to read:

Drug interaction precaution. Do not use this product if you are taking a prescription drug containing a monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), without first consulting your doctor. If you are uncertain whether your prescription drug contains an MAOI, consult a health professional before taking this product.

The agency invited comments and information on interactions between selegiline and sympathomimetic amines and asked whether, from a public health perspective, it would be appropriate to expand the drug interaction precaution statement, as indicated. Final agency action occurs with the publication of this final monograph, which is the final rule establishing a monograph for OTC nasal decongestant drug products (see comment 22 in section I.E. of this document.)

The Advisory Review Panel on OTC Oral Cavity Drug Products (Oral Cavity Panel) reviewed safety and effectiveness data on two oral nasal decongestant ingredients, phenylephrine hydrochloride and phenylpropanolamine hydrochloride (in lozenge form), and classified these nasal decongestants in Category III in its report on OTC oral health care drug products published in the **Federal Register** of May 25, 1982 (47 FR 22920). In the tentative final monograph for OTC oral health care anesthetic/analgesic, astringent, debriding agent/oral wound cleanser, and demulcent drug products published in the **Federal Register** of January 27, 1988 (53 FR 2448), the agency referred the data on these two oral nasal decongestant ingredients to the rulemaking for OTC nasal decongestant drug products because most of the nasal decongestant ingredients had been reviewed earlier and more extensively by the Cough-Cold Panel. In this final rule, phenylephrine hydrochloride for use as an oral nasal decongestant, which would include use in a lozenge dosage form, is a monograph ingredient. However, because of still unresolved safety issues concerning phenylpropanolamine preparations, the agency is deferring action on this drug. (See the **Federal Register** of January 15, 1985, 50 FR 2220 at 2221.) Therefore, phenylpropanolamine preparations will not be categorized or further discussed in this document.

Propylhexedrine was formerly a scheduled drug both domestically and internationally, but had an exclusion under 21 CFR 1308.22 that allowed it to

be sold OTC in the United States in inhaler products. In September 1990, the 27th World Health Organization (WHO) Expert Committee on Drug Dependence examined the international scheduling of propylhexedrine. Based on new data, the Expert Committee recommended to WHO that propylhexedrine be removed from international control. On June 10, 1991, the United States was notified that propylhexedrine had been decontrolled internationally, thus obviating the need for domestic control. The Drug Enforcement Administration issued a final rule in the **Federal Register** of December 3, 1991 (56 FR 61372) to remove propylhexedrine from the schedules of the Controlled Substances Act.

The ingredient l-desoxyephedrine is currently a scheduled drug in the United States. However, a specific marketed inhaler product containing this topical nasal decongestant ingredient has an exclusion that allows it to be sold OTC in the United States (see 21 CFR 1308.22). Thus, this ingredient for topical use in an inhaler dosage form could be included in this final monograph (See paragraph 19 in section II of this document.)

The agency's final rule, in the form of a final monograph, for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products is also being published in segments. Final agency action on all OTC nasal decongestant drug products, except those containing phenylpropanolamine, occurs with the publication of this final monograph, which establishes §§ 341.3(f) and (g), 341.20, and 341.80 for OTC nasal decongestant drug products in part 341 (21 CFR part 341). Combination drug products containing nasal decongestant ingredients are addressed in the tentative final monograph on OTC combination cough-cold drug products, which was published in the **Federal Register** of August 12, 1988 (53 FR 30522). A final rule for those combination products will be published in a future issue of the **Federal Register**.

The OTC drug procedural regulations (21 CFR 330.10) provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA does not use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage. In place of Category I, the term "monograph conditions" is used; in place of Category II or III, the term "nonmonograph conditions" is used.

As discussed in the proposed rule on OTC nasal decongestant drug products (50 FR 2220), the agency advised that the conditions under which the drug products that are subject to this monograph will be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication in the **Federal Register**. Therefore, on or after August 23, 1995, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application or abbreviated application (hereinafter called application). Further, any OTC drug product subject to this monograph that is repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In response to the proposed rule on OTC nasal decongestant drug products, 11 drug manufacturers, 1 drug manufacturers' association, 1 health care professional, and 11 consumers submitted comments. Copies of the comments received are on public display in the Dockets Management Branch (address above). Any additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch.

In proceeding with this final monograph, the agency has considered all comments and objections, and the changes in the procedural regulations.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notice published in the **Federal Register** of August 9, 1972 (37 FR 16029) or to additional information that has come to the agency's attention since publication of the notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch (address above).

I. The Agency's Conclusions on the Comments

A. General Comments on OTC Nasal Decongestant Drug Products

1. One comment contended that OTC drug monographs are interpretive, as opposed to substantive, regulations. The comment referred to statements on this issue submitted earlier to other OTC drug rulemaking proceedings.

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products, published in the **Federal Register** of May 11, 1972 (37 FR 9464 at 9471 to 9472); in paragraph 3 of the preamble to the tentative final monograph for OTC antacid drug products, published in the **Federal Register** of November 12, 1973 (38 FR 31260); and in paragraph 2 of the preamble to the tentative final monograph for OTC cough-cold combination drug products, published in the **Federal Register** of August 12, 1988 (53 FR 30522 at 30524). FDA reaffirms the conclusions stated in those documents. Court decisions have confirmed the agency's authority to issue substantive regulations by rulemaking. (See, e.g., *National Nutritional Foods Association* v. *Weinberger*, 512 F.2d 688, 696–98 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers* v. *FDA*, 487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd*, 637 F.2d 887 (2d Cir. 1981).)

2. Two comments stated that nasal decongestants cause dependency and should not be available OTC. One of the comments, from a physician, observed that a relatively large number of individuals with upper respiratory symptoms (often associated with allergic rhinitis) begin taking nasal decongestants and find that the symptoms persist for longer than 1 week and often persist for several months at a time. Furthermore, if the individuals attempt to use nasal decongestants for the duration of this period, there is a high likelihood that they will develop a tolerance of the nasal mucosa to the decongestant effect of the medication. When the individuals try to stop the medication, they develop a significant obstructive congestion of the nasal mucosa from which they only apparently find relief through continued use of the medicine. Also, the medication appears to lose its effect, somewhat, with continued use over a long period of time, thus requiring even more frequent use. The comment stated this was particularly a problem with

nasal sprays and cited several patients who persisted in using OTC nasal sprays every 2 hours or so despite intensive efforts by the physician to discourage such use. The comment contended that easy accessibility of these products, due to their OTC status, makes it almost impossible to wean some patients from the use of nasal decongestants. The second comment, from a consumer, opposed OTC use of nasal decongestants because of experience in which a member of the family became dependent on nasal decongestant sprays in order to breathe.

The agency has reexamined the Cough-Cold Panel's discussion regarding "rebound congestion." The Cough-Cold Panel stated the following:

> Because of the remarkable degree of nasal decongestion which follows topical application of these agents, there is the tendency on the part of patients to administer nasal decongestants too frequently and for too long a period of time. Continued and intense drug-induced vasoconstriction can lead to rebound dilation of the blood vessels as the drug effect subsides. This phenomenon, which intensifies nasal congestion and perpetuates the rhinitis condition, has been termed "rebound congestion." This problem is minimized if topically applied decongestants are administered in accordance with label directions at recommended intervals for periods not exceeding 3 days. (See 41 FR 38312 at 38396.)

Although aware that continued use of nasal decongestant drugs might result in rebound congestion, the Cough-Cold Panel thought that the clinical and marketing data it reviewed showed these drugs to be safe and effective when used according to label directions. Therefore, the Cough-Cold Panel concluded that such drugs should be available for OTC use and it recommended the following warning: "Do not use this product for more than 3 days. If symptoms persist, consult a physician" (41 FR 38312 at 38423).

In the tentative final monograph, the agency concurred with the Cough-Cold Panel's recommendations that all nasal drops, sprays, and jellies, and propylhexedrine in inhalant form be labeled to limit use to not more than 3 days so as to discourage prolonged use and that a doctor should be consulted if symptoms persisted after 3 days of use. (See § 341.80 (c)(2)(iii)(*a*) and (c)(2)(vi) in 50 FR 2220 at 2239.) The ingredient l-desoxyephedrine in inhalant form had to bear the same warning except it stated 7 days instead of 3 days. (See § 341.80(c)(2)(ii) and discussion in 50 FR 2220 at 2225.)

In addition, the agency has reviewed comments to the Cough-Cold Panel's report concerning rebound congestion and finds seven comments from allergists who specifically mentioned oxymetazoline, xylometazoline, naphazoline, or phenylephrine as causing rebound congestion due to prolonged or excessive use (Ref. 1). Moreover, the agency has reviewed adverse drug reaction reports for the years 1976 to 1993 and finds that the two most frequently reported adverse effects of marketed OTC topical nasal decongestant drug products are rebound congestion and drug dependence (Ref. 2).

The agency believes that the OTC availability of topical nasal decongestants is beneficial to many consumers who seek temporary relief from nasal congestion and concurs with the Cough-Cold Panel's recommendations that these products can be safely used according to label directions. The agency is concerned, however, in view of comments submitted to this rulemaking and adverse drug reactions reported to FDA, that consumers may not be adequately alerted and warned of the problem of rebound congestion, which may be caused by prolonged or excessive use of these preparations. Thus, the agency believes that the 3-day use warning should be expanded to explain to consumers the reason for the 3-day limitation for use of topical nasal decongestants.

Therefore, in this final monograph the warning in § 341.80(c)(2)(iii)(A) for adults, in § 341.80(c)(2)(viii) for children under 12 years of age, and in § 341.80 (c)(2)(v) and (c)(2)(ix) for propylhexedrine in inhalant form for adults and children, respectively, is expanded as follows: "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor."

The agency concludes that these additions to the labeling included in this final monograph will provide for the safe and effective use of OTC topical nasal decongestant drugs.

References

(1) Comments No. C0026, C0077, C0092, C0095, C0118, C0120, C0130, Docket No. 76N–0052, Dockets Management Branch.

(2) Department of Health and Human Services, Food and Drug Administration, "Spontaneous Reporting System, Line Listing of Adverse Reports: Nasal–76–93," 1976–1993, in OTC Vol. 04NFM, Docket No. 76N–052N, Dockets Management Branch.

3 Referring to the statements in the tentative final monograph for OTC antihistamine drug products, "* * * antihistamines did not reduce nasal obstruction and therefore did not aid in sinus drainage. To the contrary, the studies indicated that antihistamines may sometimes further aggravate nasal obstruction" (50 FR 2200 at 2203), one comment expressed concern that FDA not use this statement as a basis for disagreeing with the Cough-Cold Panel's Category I classification of combinations containing an antihistamine and an oral nasal decongestant.

In the tentative final monograph for OTC antihistamine drug products (50 FR 2200 at 2203), the agency made the statements quoted above as part of its discussion that antihistamines are ineffective for the treatment of sinus congestion. It was not the agency's intent to use the statements as a basis for disagreeing with combination drug products containing an antihistamine and an oral nasal decongestant.

In the tentative final monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic combination drug products, the agency agreed with the Cough-Cold Panel's Category I classification of combinations containing an antihistamine and an oral nasal decongestant (53 FR 30522 at 30539). In view of the data reviewed by the Cough-Cold Panel that support combinations containing an antihistamine and an oral nasal decongestant (41 FR 38312 at 38326) and the extensive data on such combinations that are available to the agency, the agency reiterates the Cough-Cold Panel's recommendation that combinations containing an antihistamine and an oral nasal decongestant are safe, effective, and rational.

B. Comments on Switching Prescription Nasal Decongestant Active Ingredients to OTC Status

4. Several comments opposed the availability of oxymetazoline hydrochloride and xylometazoline hydrochloride as OTC topical nasal decongestants. The comments also opposed the availability of pseudoephedrine hydrochloride and pseudoephedrine sulfate at dosage levels twice as high as previously permitted for OTC use. The comments expressed concern that these drugs could be dangerous or harmful to many people, young and old alike. One comment felt that self-medicating with nasal decongestants might cause damage to "mucous-lined passages" and that consumers might not know if they have one of the conditions (i.e., heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland) listed in the warnings for these

products. Two comments approved of FDA's requirement for warning information in labeling and supported the OTC availability of these drugs. Another comment mentioned, however, that many persons unfortunately do not or cannot read labels.

As discussed in the tentative final monograph, the agency reviewed safety and effectiveness data on oxymetazoline hydrochloride, xylometazoline hydrochloride, pseudoephedrine hydrochloride, and pseudoephedrine sulfate and agreed with the Cough-Cold Panel that these active ingredients could be generally recognized as safe and effective for OTC use when appropriately labeled. (See 50 FR 2220 at 2222 to 2223, 2229 to 2230, and 2233 to 2234.) The comments did not submit any data to show that these ingredients should not be available OTC.

To enhance the safe use of these ingredients, in the tentative final monograph, the agency modified several of the Cough-Cold Panel's recommendations regarding pseudoephedrine hydrochloride and pseudoephedrine sulfate as oral nasal decongestants, and oxymetazoline hydrochloride and xylometazoline hydrochloride as topical nasal decongestants. For example, the agency reduced the maximum adult oral dosage of pseudoephedrine preparations from 360 milligrams (mg) to 240 mg in 24 hours (50 FR 2229 to 2230). The agency also proposed that topical nasal decongestant products containing oxymetazoline hydrochloride and xylometazoline hydrochloride not be used in children under 6 years of age unless recommended by a doctor (50 FR 2222 to 2223).

Regarding one comment's concern that self-medicating with OTC nasal decongestants might cause damage to "mucous-lined passages," the comment did not explain its use of the term "mucous-lined passages," nor did it submit any data to substantiate its claim that OTC nasal decongestants at the recommended dosages can cause damage to "mucous-lined passages." Although frequent and prolonged use of topical nasal decongestants may lead to rebound congestion (see comment 2 in section I.A. of this document), the agency is unaware of possible long-term damage to "mucous-lined passages" if a topical nasal decongestant drug product is used for a short period of time and according to directions. As the Cough-Cold Panel pointed out, the problem of rebound congestion is not a factor with use of the orally administered nasal decongestants (41 FR 38312 at 38397).

Regarding the comment's concern that consumers might not know if they have one of the conditions listed in the warnings for these products (i.e., heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland), the agency notes that there are additional warnings in the monograph informing consumers that topical nasal decongestants should not to be used for more than 3 days and that oral nasal decongestants should not be used for more than 7 days, and if symptoms persist, to consult a doctor. Because these products are intended to be used for a limited time only, the agency believes that the risk of adverse effects at the recommended oral or topical dosages is minimal. Moreover, the agency believes that persons having most of the conditions listed in the warning (heart disease, thyroid disease, diabetes, difficulty in urination) would be aware of their condition (because of other apparent symptoms) and be under medical treatment, and the warning instructs them not to use the product unless directed by a doctor.

There is a concern, however, for individuals having certain conditions that may have no apparent symptoms. High blood pressure is a well-known example of such a disease. Persons with high blood pressure may be unaware that they have the condition and may use a nasal decongestant without being aware that the nasal decongestant drug can affect the condition. Nasal decongestants and other sympathomimetic drugs can produce a variety of adverse effects and should be used with caution in individuals with high blood pressure (Refs. 1 and 2). Of the estimated 58 million hypertensive individuals in the United States, about 20 percent (approximately 11 million) do not know they have high blood pressure (Ref. 3). If high blood pressure is not treated, problems such as heart failure, stroke, and kidney disease may occur. The agency believes that periodic medical examinations, high blood pressure screening programs, and education are the most important tools to detect undiagnosed hypertensive individuals. The agency encourages consumers to take advantage of such programs to help minimize the risks associated with undiagnosed high blood pressure.

Regarding the comment that many persons unfortunately do not or cannot read labels, the agency notes that section 502(c) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352(c)) requires that a drug be labeled "* * * in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use." The labeling in this final monograph is intended to meet this statutory requirement.

The safety and effectiveness data on oxymetazoline hydrochloride, xylometazoline hydrochloride, pseudoephedrine hydrochloride, and pseudoephedrine sulfate that were reviewed by the Cough-Cold Panel and the agency support the agency's conclusion that these ingredients can be generally recognized as safe and effective for OTC use when marketed in accordance with the labeling and other conditions established in this final monograph.

References

(1) Berkow, R., editor, "The Merck Manual," 16th ed., Merck and Co., Rahway, NJ, p. 192, 1992.

(2) "Drug Evaluations Annual," American Medical Association, Milwaukee, WI, pp. 407–408, 1991.

(3) Berkow, R., editor, "The Merck Manual," 16th ed., Merck and Co., Rahway, NJ, p. 419, 1992.

C. Comments on Specific OTC Nasal Decongestant Active Ingredients

5. One comment requested that the agency place camphor (0.1 percent), eucalyptus oil (0.025 percent), and menthol (0.05 percent) in Category I as individual OTC topical/inhalant nasal decongestants for use in a hot steam vaporizer; and place the ingredients camphor (4.73 to 5.3 percent), eucalyptus oil (1.2 to 1.3 percent), and menthol (2.6 to 2.8 percent) in Category I as individual OTC topical/inhalant nasal decongestants for use in a chest rub ointment form. The comment submitted three controlled clinical studies (CRD 83–10, CRD 82–10, and CRD 82–09) and two pilot clinical studies (CRD 74–63A and CRD 75–39) of the individual ingredients to support its request (Ref. 1). The first study (CRD 83–10) concerned the single aromatics in steam from a vaporizer. The other four studies concerned the single aromatics in petrolatum applied to the chest and throat. In response to the agency's concerns regarding the statistical analysis of study CRD 83–10 (Ref. 2), the comment provided a statistical reanalysis of the study (Ref. 3).

The agency has reviewed the data and determined that the clinical studies do not support the reclassification of the individual ingredients as requested by the comment. Although one study (CRD 83–10) shows some statistically significant evidence of the effectiveness of camphor, eucalyptus oil, and menthol as topical/inhalant nasal decongestants administered by steam vaporization, there are certain statistical problems

with the data that make the results questionable. Although the statistical reanalysis provides some statistical evidence of efficacy, the agency concludes that stronger evidence of efficacy from a second study is needed (Ref. 4). The other four studies (CRD 82–10, CRD 82–09, CRD 74–63A, and CRD 75–39) are insufficient to demonstrate the effectiveness of camphor, eucalyptus oil, and menthol as individual topical/inhalant nasal decongestants in a chest rub ointment form.

Study CRD 83–10 was designed to determine the individual topical/inhalant nasal decongestant effect of camphor, eucalyptus oil, and menthol vaporized in steam compared to unmedicated steam. In this single-blind, parallel study, 234 subjects with acute upper respiratory tract infection were equally divided into 4 treatment groups (vaporized camphor, eucalyptus oil, menthol, or steam control). Nasal airway resistance was measured with a rhinomanometer before treatment, every 15 minutes (min) for the first hour and every 30 min for the second hour. The investigator reported that when the individual observation time points were examined, the results indicated that each ingredient was significantly more effective in reducing nasal congestion than steam alone at each 15-min interval over the first hour (all $p \leq 0.02$) and over the entire 2-hour exposure period.

Although the comment claimed that study CRD 83–10 showed each active ingredient to be statistically better than placebo (steam) control, the agency has determined that the data and the reanalysis of study CRD 83–10 alone do not provide adequate support for the monograph status of camphor, eucalyptus oil, and menthol as individual topical/inhalant nasal decongestant ingredients for several reasons. First, there was an improper use of baseline values; for example, the baseline values were measured 15 min and 0 min before treatment, but only the 0-minute measurement was used as the baseline value. Conversely, in study CRD 82–10, the baseline values were taken as the average of 15- and 0-min pretreatment measurements. Second, the use of the Bartlett's test to verify the assumption of homogeneity of the variances in the logarithm-transformed data demonstrated that the homogeneity of the variances was found to be acceptable for only the first 60 min, i.e., variances among treatment groups were not significantly different for the periods of 15, 30, 45, and 60 min. However, statistically significant differences were found at 90 min, 120 min, and overall, with the steam control group showing an unacceptable consistently higher variance than the active ingredient treatment groups. Third, the reanalysis of the logarithm-transformed rhinomanometer measurement data by the Kruskal-Wallis test (a nonparametric test) showed that the active ingredients were statistically better than the steam control group only within the first hour of the study and not significantly better than the steam control group after one hour. These weak findings would be further weakened if adjustment for p-value for multiple testing of time points were made.

Should another study be done, a repeated measurement analysis (i.e., an overall analysis) of the rhinomanometer data needs to consider the increase in variance over all time points to remedy the problem of repeated testings. Further, if variances in results increase over the time period in an additional study, the reason for this occurrence needs to be addressed.

Study CRD 82–10 compared the nasal decongestant effects of the individual ingredients camphor 5.2 percent, eucalyptus oil 1.3 percent, and menthol 2.8 percent in petrolatum against a petrolatum placebo in 40 subjects per group with acute coryzal rhinitis (common cold) using a randomized parallel design. The investigator reported that there were no statistically significant differences between treatments with respect to objectively measured nasal congestion for the total study population. Study CRD 82–09 used the same protocol as CRD 82–10, with 39 to 42 subjects per group. This study also did not show any statistically significant differences between test and control treatments. In conclusion, both studies, CRD 82–10 and CRD 82–09, provide no statistically significant data that the individual active ingredients were better than petrolatum control in reducing nasal congestion in subjects with acute coryzal rhinitis.

Regarding the two pilot studies (CRD 74–63A and CRD 75–39), the agency notes that both studies used the same protocol. The studies were randomized crossover studies using subjects with colds. Comparisons were made by objective measurement of nasal airway resistance using anterior rhinomanometry. Study CRD 74–63A compared a commercial product containing a combination of volatile aromatic oils with the following individual ingredients: Eucalyptus oil 1.33 percent in a petrolatum base, turpentine oil 5.12 percent in a petrolatum base, and petrolatum (placebo). Study CRD 75–39 compared the nasal decongestant effects of a commercial product containing a combination of volatile aromatic oils with the following individual ingredients: Camphor 4.7 percent in a petrolatum base, menthol 2.6 percent in a petrolatum base, and petrolatum (placebo). A summary statistical analysis of studies CRD 74–63A and CRD 75–39, prepared by the comment's statistician (Ref. 2), states that these studies show no statistical advantages for the components over petrolatum and that the absence of statistical significance in these studies is not unexpected because of the small sample sizes of the treatment groups. Furthermore, significant residual effects were detected in the data from these studies, indicating that the crossover model was inappropriate. The agency concludes that studies CRD 74–63A and CRD 75–39 do not provide adequate data to demonstrate the effectiveness of camphor, eucalyptus oil, and menthol as individual topical/inhalant active ingredients when administered in a chest rub ointment form.

In conclusion, the submitted data are insufficient to generally recognize camphor, eucalyptus oil, and menthol as safe and effective as individual topical/inhalant nasal decongestant active ingredients, either in petrolatum applied to the chest and throat or in a hot steam vaporizer. Therefore, at this time, these ingredients for these uses are not being included in the final monograph for OTC nasal decongestant drug products. Combination products containing these ingredients are discussed in the tentative final monograph for OTC cough-cold combination drug products, published in the **Federal Register** of August 12, 1988 (53 FR 30522). In that tentative final monograph nasal decongestant use was discussed in comment 59 (53 FR 30522 at 30550), and antitussive use was discussed in comments 56 and 57 (53 FR 30522 at 30547 to 30548). These combination products will be addressed in the final monograph for OTC cough-cold combination drug products, which will be published in a future issue of the **Federal Register**.

The agency's detailed comments and evaluations of the data are on file in the Dockets Management Branch (Ref. 3).

References

(1) "VapoRub," Vol. 1, Richardson-Vicks, Inc., submitted as part of Comment No. C0212, Docket No. 76N–052N, Dockets Management Branch.

(2) Letter from W. E. Gilbertson, FDA, to E. J. Hanus, Richardson-Vicks, Inc., coded as LET095, Docket No. 76N–052N, Dockets Management Branch.

(3) Letter from E. J. Hanus, Richardson-Vicks, Inc., to W. E. Gilbertson, FDA, coded as LET096, Docket No. 76N–052N, Dockets Management Branch.
(4) Letter from W. E. Gilbertson, FDA, to E. J. Hanus, Richardson-Vicks, Inc., coded as LET109, Docket No. 76N–052N, Dockets Management Branch.

6. One comment submitted data (Refs. 1 and 2) to support the effectiveness of ephedrine and its salts as an oral nasal decongestant. The data consisted of four studies (CRD 78–04, CRD 78–06, CRD 78–26, and CRD 78–27) (Refs. 3 through 6) in which the data were pooled and analyzed as one study; three single-investigator studies (CRD 74–9, CRD 74–57, and CRD 76–61) (Refs. 7, 8, and 9); and four articles from the scientific literature (Refs. 10 through 13). Additional statistical information (Ref. 2) was provided by the comment in response to the agency's request (Ref. 14). The comment also noted that the agency concluded in the tentative final monograph for OTC bronchodilator drug products (47 FR 47520 at 47527, October 26, 1982) that ephedrine and its salts at a 25-mg oral dose as a bronchodilator are safe for OTC use. The comment requested that ephedrine and its salts be placed in Category I for oral nasal decongestant use at a dosage of 8 to 25 mg every 4 hours, not to exceed 75 mg in 24 hours.

The pooled study (studies CRD 78–04, CRD 78–06, CRD 78–26, and CRD 78–27) (Refs. 3 through 6) involved a total of 445 subjects obtained by 4 different investigators. These were parallel studies with 60 subjects participating in CRD 78–04, 54 subjects in CRD 78–06, 202 subjects in CRD 78–26, and 129 subjects in CRD 78–27. Each study group was subdivided into three subgroups. The subjects in each subgroup received a single dose of aqueous solution containing ephedrine sulfate 8 mg/dose, ephedrine sulfate 12 mg/dose, or an aqueous placebo. Nasal airway resistance was measured by Vick's Rhinomanometer at 30, 60, 90, 120, and 180 min after the dose was given.

In analyzing the data in the pooled study, the agency noted that out of the four studies, there were only sporadic statistically significant rhinomanometer data differences in favor of ephedrine 12 mg over placebo in Study CRD 78–26 (Ref. 5). For subjective subject ratings of nasal congestion, there were only sporadic statistically significant differences in favor of ephedrine 12 mg over placebo in Study CRD 78–26. With sample sizes ranging from 17 to 45 subjects per treatment group, there should be adequate statistical power to detect a significant clinical difference if it exists. However, both rhinomanometer measurements and subject ratings of nasal congestion data failed to clearly differentiate ephedrine from placebo in these studies.

In the pooled data analysis, significant treatment by center interaction was found in 3 of the 5 time-point analyses ($p \leq 0.15$). Six of 25 time-point analyses (24 percent) showed that placebo was the same or better than ephedrine. A statistical reanalysis of the data (Ref. 2) did not establish any statistical evidence, either in the pooled data or in any of the individual studies, that ephedrine is superior to the placebo control in reducing nasal congestion. The agency also notes that this reanalysis of the data using the Kruskal-Wallis test (a nonparametric version of "one-way" analysis of variance) does not remove the issue of center interaction. Further, the mathematical model that was used to analyze the rhinomanometer data provides an extremely low R-square value. Hence, the agency considers these findings as casting doubt on the poolability of these efficacy data and believes that conclusions should be drawn based on the results from individual studies. Therefore, the agency concludes that the data in the pooled study fail to provide substantive statistical evidence of effectiveness.

The single-investigator studies (CRD 74–9, CRD 74–57, and CRD 76–61) (Refs. 7, 8, and 9) involved a total of 316 subjects. Study CRD 74–57 (Ref. 8) did not show any statistically significant difference between ephedrine and placebo. This parallel-design, double-blind, computer-randomized study used nasal airway flow rate measurements to compare the nasal decongestant effect of solutions of ephedrine sulfate 8 mg/30 milliliters (mL), ephedrine sulfate 16 mg/30 mL, phenylpropanolamine hydrochloride 37.5 mg/30 mL, and a 30 mL placebo vehicle solution containing no active ingredient. Two doses were given, 4 hours apart. A total of 189 subjects with nasal congestion due to coryza was divided among the 4 treatment groups. The results showed that the phenylpropanolamine solution had the greatest effect on increasing nasal airflow when compared with both doses of ephedrine and the placebo. Both doses of ephedrine produced significantly greater flow than placebo overall, but not at any of the individual time intervals. The effect of ephedrine 16 mg/30 mL also approached significance at the final evaluation (2 hours after the second dose). There were no significant differences noted in the subjective evaluation of runny nose, post-nasal drip, watery eyes, and number of sneezes. However, the use of the ephedrine 16 mg/30 mL solution seemed to be beneficial in reducing the number of "nose blows."

Study CRD 74–9 (Ref. 7) also did not demonstrate any statistically significant difference between ephedrine and placebo. This was a parallel-design study employing 86 subjects with nasal congestion due to coryza. The subjects were divided into 3 subgroups with 29 subjects receiving ephedrine sulfate 8 mg/30 mL (aqueous vehicle), 29 subjects receiving phenylpropanolamine hydrochloride 25 mg/30 mL (aqueous vehicle), and 28 subjects receiving 30 mL of the aqueous vehicle alone. It was noted in this study that sorbitol was added to the test solution given to the first 34 subjects. However, when 3 subjects (1 in each of the 3 treatment groups) experienced intestinal distress, the remaining 52 subjects were given an aqueous test solution without the sorbitol. The agency notes that, in general, no clinical conclusions can be derived from this study because of the differing results obtained between the sorbitol and nonsorbitol-containing test solutions.

Only one study, CRD 76–61 (Ref. 9), showed some favorable results. This study was a double-blind, computer-randomized crossover study involving 41 subjects having nasal congestion due to coryza. Eighteen subjects received 8 mg of ephedrine sulfate and 23 subjects received 12 mg of ephedrine sulfate on one of two test days, both administered in 30 mL of aqueous vehicle. All 41 subjects received aqueous vehicle placebo on the other test day. Nasal airway resistance was used as an objective measure of nasal congestion and changes therein. Resistance was measured by Vick's Rhinomanometer before treatments were administered and at 30, 60, 90, 120, and 180 min after treatments, which were 24 hours apart. Subjective ratings were also recorded before each measurement. Subjectively, subjects using the 8-mg and 12-mg doses of ephedrine sulfate perceived an improvement in nasal decongestion to a statistically significant extent, but the comparisons with placebo results were not significant. As determined by nasal airway resistance measurements, both the 8-mg and 12-mg doses of ephedrine sulfate decreased the nasal congestion of subjects to a statistically significant extent overall, in comparison with the results obtained with the placebo. However, the agency considers the results of the study to be inconsistent because the ephedrine 8-mg group obtained some favorable results over placebo at 60 min after treatment, but the ephedrine 12-mg group obtained

only sporadically favorable results. In addition, the 12-mg group obtained significant results only within the first hour after treatment, while the 8-mg group did not obtain significant results until 1 hour after treatment. These discrepancies are not adequately explained. The agency believes that the findings in both the pooled studies (Refs. 3 through 6) and the individual study CRD 76–61 (Ref. 9) would be further weakened if adjustments for multiple testings of hypotheses were made.

With regard to the four articles (Refs. 10 through 13) from the literature, the agency finds that these articles are not supportive of either the pooled study or the individual studies. The McLaurin, Shipman, and Rosedale study (Ref. 10) was reviewed by the Cough-Cold Panel, which found that it did not contain any conclusive data to support claims of nasal decongestant effectiveness for 8 to 12 mg ephedrine doses contained in OTC drug products (41 FR 38312 at 38408). Although the Cough-Cold Panel stated that the study demonstrated nasal decongestant effectiveness of orally administered ephedrine sulfate in doses of 25 mg, the agency considers the study inadequate to establish effectiveness because it was not controlled. The study by Gowen and Nedzel (Ref. 11) and the study by Mothersill (Ref. 12) are not adequate because the results were subjective and ephedrine was not studied alone, but in combination with other active ingredients. Likewise, the Aschan study (Ref. 13) also was not a single active ingredient study.

Although safety is not a problem, as the comment noted, based on the lack of adequate data to demonstrate effectiveness, ephedrine and its salts are not being included as oral nasal decongestant ingredients in this final monograph. The agency's detailed comments and evaluation of the data are on file in the Dockets Management Branch (Ref. 15).

References

(1) Comment No. C0214, Docket No. 76N–052N, Dockets Management Branch.

(2) Comment No. SUP003, Docket No. 76N–052N, Dockets Management Branch.

(3) Hayes, S.L., "Multicenter-Pooled Study," draft of unpublished study (CRD 78–04), in Comment No. C0214, Docket No. 76N–052N, Dockets Management Branch.

(4) Fulco, O.J., "Multicenter-Pooled Study," draft of unpublished study (CRD 78–06), in Comment No. C0214, Docket No. 76N–052N, Dockets Management Branch.

(5) doPico, G.A., "Multicenter-Pooled Study", draft of unpublished study (CRD 78–26), in Comment No. C0214, Docket No. 76N–052N, Dockets Management Branch.

(6) Diamond, P.H., "Multicenter-Pooled Study," draft of unpublished study (CRD 78–27), in Comment No. C0214, Docket No. 76N–052N, Dockets Management Branch.

(7) Connell, J.T., "Ephedrine, Phenylpropanolamine, and Placebo Comparisons," draft of unpublished study (CRD 74–9), in Comment No. C0214, Docket No. 76N–052N, Dockets Management Branch.

(8) Connell, J.T., "Nasal Airway Flow Rate Measurement Comparisons," draft of unpublished study (CRD 74–57), in Comment No. C0214, Docket No. 76N–052N, Dockets Management Branch.

(9) doPico, G.A., "Ephedrine and Placebo Comparison," draft of unpublished study (CRD 76–61), in Comment No. C0214, Docket No. 76N–052N, Dockets Management Branch.

(10) McLaurin, J.W., W.F. Shipman, and R. Rosedale, "Oral Decongestants—A Double Blind Comparison Study of the Effectiveness of Four Sympathomimetic Drugs: Objective and Subjective," *Laryngoscope*, 71:54–67, 1961.

(11) Gowen, G.H., and A.J. Nedzel, "Effectiveness of the Oral Administration of Ephedrine in the Common Cold," *Illinois Medical Journal*, 71:132–136, 1937.

(12) Mothersill, M.H., "Treatment of Hay Fever with a Combination of a Sympathomimetic and an Antihistaminic Drug," *Annals of Allergy*, 8:223–228, 1950.

(13) Aschan, G., "Decongestion of Nasal Mucous Membranes by Oral Medication in Acute Rhinitis," *Acta Otolaryng*, 77:433–438, 1974.

(14) Letter from W.E. Gilbertson, FDA, to E.J. Hanus, Richardson-Vicks, coded LET020, Docket No. 76N–052N, Dockets Management Branch.

(15) Letter from W.E. Gilbertson, FDA, to E.J. Hanus, Richardson-Vicks, coded LET107, Docket No. 76N–052N, Dockets Management Branch.

7. One comment submitted a citizen petition requesting that 10 mg menthol in a solid dosage form for use as a topical/inhalant nasal decongestant be included in the final monograph (Refs. 1 and 2). The comment requested the following directions for use for the 10-mg menthol solid dosage form: "Adults and children 3 to under 12 years of age: dissolve one solid dosage form in the mouth every 2 hours as needed. Do not chew. Children under 3 years of age: consult a doctor."

The agency has reviewed the petition and other information and finds the data supportive of the effectiveness of a 10-mg menthol lozenge as a single dose for topical nasal decongestant use. However, the agency has concluded that the data are not sufficient to include the ingredient in the monograph for the reasons discussed below.

The petition included a double-blind, randomized, placebo-controlled, parallel-design, single-dose study of a 10-mg menthol lozenge in subjects with viral rhinitis. The subjects were at least 18 years of age with symptoms of stuffy nose, runny nose, sneezing, and/or cough of no more than 48 hours duration. The objective of the study was to determine if statistically significant decreases in nasal airway resistance occurred at specific intervals after administration of the drug. Posterior rhinometry measurements were correlated with the subjects' subjective ratings of decongestant activity. Measurements of nasal flow/resistance were made 5 min before and immediately prior (0 min) to administration of the test lozenge and at 15, 30, 60, 90, and 120 min after dosing. The measurement immediately prior to dosing was used as the baseline measurement. The nasal/flow resistance data were analyzed by a repeated measures analysis of variance with 6 time points (baseline, 15, 30, 60, 90, and 120 min) as the repeat factor. Changes from the baseline at the post-treatment time points were also analyzed using a one-way analysis of variance.

The agency notes that the protocol for this study is similar to that proposed by the Panel (41 FR 38312 at 38415). The Cough-Cold Panel recommended that a study to show effectiveness of a nasal decongestant drug should be a double-blind, placebo-controlled assessment of the drug's ability to decrease nasal airway resistance. The Cough-Cold Panel also considered subjective assessment by the subjects to be desirable. The Cough-Cold Panel stated that where rebound congestion with repeated use is a concern, labeling should specify short-term use in providing temporary relief of symptoms. The Cough-Cold Panel recommended that specific data be obtained by testing the nasal decongestant in the concentrations and maximal dosage frequencies to be recommended for periods of at least 1 week to address the incidence and severity of a drug-induced increase in nasal airway resistance. The Cough-Cold Panel required two positive studies based on the results of two different investigators or laboratories to show effectiveness.

The agency finds that the results of the study suggest that 10 mg menthol in a solid dosage form is effective in the relief of nasal congestion due to viral rhinitis. However, the repeated measures analysis of variance results were not informative because they

included the baseline levels in the analysis. By deleting the baseline levels from the analysis, the agency notes that the multivariate analyses of the data using the Statistical Analysis System Institute statistical system showed a significant treatment effect but nonsignificant time and treatment by time interaction. The results of the study support a 2-hour duration of action from a single dose. However, because the proposed directions for the product include multiple doses (i.e., "every 2 hours as needed"), another study involving multiple doses is needed to support effectiveness. The study needs to be done using the same dosage with the drug given at the same time intervals as proposed for the label directions. A 3-day study is necessary to show effectiveness as a nasal decongestant if the product will be indicated for colds and 7 days if indicated for allergies.

The agency notes that the petition did not address the potential problem of rebound congestion occurring with repeated use of menthol lozenges. In the tentative final monograph (50 FR 2220 at 2233), the agency discussed the occurrence of rebound congestion resulting from topical nasal decongestants in a lozenge or mouthwash dosage form. The agency stated that when ingredients such as menthol are administered in the form of lozenges, rebound is unlikely to occur and that it may be more appropriate to use a 7-day warning, i.e., "Do not use this product for more than 7 days," rather than a 3-day warning. However, because such lozenges are not included in this final monograph, such a warning requirement is not applicable at this time. The agency believes that the potential for rebound congestion to occur should be studied in any multi-dose study, such as the study discussed above, involving topical nasal decongestants in a lozenge or mouthwash dosage form to rule out the potential for rebound congestion to occur and to determine which warning statement would be appropriate to use for the product.

Based on the above information, the agency is not including 10 mg menthol in solid dosage form as a topical nasal decongestant in this final monograph. The agency's detailed comments and evaluations on the data are on file in the Dockets Management Branch (Ref. 3).

References

(1) Comment No. CP00010, Docket No. 76N–052N, Dockets Management Branch.

(2) Letter from C.A. Sloughfy, Jr., Beecham Products, to J.R. Gebert, FDA, coded as LET101, Docket No. 76N–052N, Dockets Management Branch.

(3) Letter from W.E. Gilbertson, FDA, to B. Misek, Beecham Products, coded as LET108, Docket No. 76N–052N, Dockets Management Branch.

8. One comment objected to the agency's proposal in the tentative final monograph to restrict to professional labeling the use of oxymetazoline hydrochloride in children under 6 years of age because this action would exclude such use from general consumer labeling. Referring to studies that showed substantial differences when oxymetazoline was given to dogs intranasally and intravenously to elicit a cardiovascular effect (i.e., increase in blood pressure), the comment stated that the amount of oxymetazoline required to elicit any systemic effect by the intranasal route would be virtually unachievable with marketed products. Thus, according to the comment, it would be extremely unlikely that a child could receive a dose of oxymetazoline that would have systemic effects. In addition, the comment stated that a review of the company's adverse experience files showed no cardiovascular side effects from oxymetazoline that were not associated with significant overuse (either in frequency of use, quantity of use, or both). The comment added that a tabulation of the company's and FDA's adverse reaction files for oxymetazoline for the period 1975 to 1989 showed only three cases of adverse reactions in children. The comment stated that the scarcity of adverse reaction experiences demonstrates that there is no safety problem. Further, the comment contended that limiting pediatric formulations (0.025 percent) of oxymetazoline to professional labeling (excluding use from consumer labeling) is inappropriate because an OTC drug must first be available to consumers with proper labeling before professional labeling can apply. The comment contended that the agency's justification for placing 0.025 percent oxymetazoline in professional labeling, i.e., that there is a theoretical possibility of a young child swallowing excessive amounts of a potent long-acting drug due to difficulty in administering accurate dosages, is unfounded. The comment stated that if this problem does exist, it would also be a problem with the shorter acting topically applied nasal decongestant drug products because these shorter acting drug products are administered more often. If this is the case, according to the comment, then the shorter acting drug products labeled for use in young children should be labeled with the same age restrictions as proposed for oxymetazoline.

With respect to the agency's concern that it is difficult to measure the correct dose in a small child and that the child may receive an excessive dose by swallowing the administered medication (50 FR 2220 at 2230), the comment contended that drops are more easily administered than sprays. The comment stated that drops are sufficiently accurate to assure safe use in children and that, to the best of its knowledge, all pediatric formulations (0.025 percent) of oxymetazoline are marketed for use as drops, not sprays. The comment noted, specifically, that the orifice of the dropper of its oxymetazoline pediatric nasal drops drug product is controlled so that it consistently delivers an average drop volume of 0.028±0.008 mL. The comment argued that this additional safety feature further assures the accuracy of the dose. The comment concluded that it is extremely unlikely that a child could receive a dose of oxymetazoline that would have a systemic effect, even if the child inadvertently swallowed some of the drops.

The comment maintained that restricting pediatric use of oxymetazoline to professional labeling will not ease the task of measuring a correct dose, nor will it cause a young child to swallow any less of a nasal solution than he/she otherwise would. The comment contended that dosing concerns can be addressed by consumer labeling. For example, instructions for use in children might include a provision that if less than a full dose is delivered on the first try, no further attempt to readminister the drug should be made. Additionally, an alternative safeguard could be provided by restricting the amount of drug that a dropper can deliver, i.e., a safety dropper can be designed to deliver approximately 6 drops which corresponds to the labeled maximum dose of 3 drops in each nostril under conditions of normal use. The comment concluded that the agency should accept the Panel's recommendation to permit consumer labeling for oxymetazoline for children 2 to under 6 years of age.

The agency has reviewed its adverse reaction reports for oxymetazoline covering the period from 1969 to the present (Ref. 1). Only five adverse reactions in children under 8 years of age have been reported. Six adverse reactions involving xylometazoline in children under 8 years of age have been reported to the agency since 1970 (Ref.

2). Except for a single death (without sufficient detail to attribute cause in a 3-month-old male who presented a history consistent with sudden infant death syndrome), all affected children recovered soon after discontinuation of the medication. The reported reactions are generally of expected events (i.e., excitation, agitation) or involve concomitant medications associated with the reactions (e.g., antihistamines and sleepiness, or a previous history of rash from an antibiotic). Considering the long marketing history and the extent of the use of topical oxymetazoline and xylometazoline, the agency considers the number and severity of the reported cases to be very low.

Biesalski and Marquart (Ref. 3) evaluated the nasal decongestant effect of xylometazoline hydrochloride (0.1 and 0.01 percent) in 72 infants aged 5 days to 14 months, 3 premature infants, and 42 children. An additional group of 48 infants was given xylometazoline in concentrations ranging from 0.0005 to 0.005 percent. The investigators measured blood pressure in 11 children and monitored cardiac activity in 69 infants and found no effects caused by the drug. Four infants with congenital heart defects had no side effects on the heart or circulation from the drug. The investigators stated, "No side effects of any kind were noted, even in premature infants or in infants with cardiac conditions."

Based on this safety profile and the ability to control the amount of drug administered per drop or spray, the agency concludes that limiting information on the topical use of oxymetazoline and xylometazoline in children 2 to under 6 years of age to professional labeling only is unwarranted. This type of limitation would not eliminate the dangers of misuse and overuse in this age group. The agency agrees with the comment that the risk of overdose or misuse can be adequately handled by the use of a dropper or spray that is designed to restrict the amount of drug delivered to a maximum allowable dose and by appropriate OTC labeling directions and warnings.

The United States Pharmacopeia discusses calibrated dropper specifications where accuracy of dosage is important. The volume error incurred in measuring any liquid by means of a calibrated dropper should not exceed 15 percent under normal use conditions (Ref. 4). The agency is incorporating this standard for a calibrated dropper in the final monograph. The agency believes that this criterion will help assure an accurate dose and minimize the risk of overdose.

To further emphasize to consumers the importance of proper administration and the dangers of overdose in children in this age group, the agency is incorporating the following statement in the directions: "Use only recommended amount." The agency recognizes that the warnings for these two drugs already include the statement "Do not exceed recommended dosage." Nonetheless, the agency believes that an additional statement in the directions sections will reinforce the importance of not using an excessive amount of drug. The agency also believes that the warning not to exceed the recommended doses within a 24-hour period will provide an additional safeguard against overdosing. The agency is requiring that both of these statements appear in product labeling in boldface type.

Accordingly, the agency is adding new sections for oxymetazoline hydrochloride (§ 341.80(d)(2)(iv)(A)(*2*)) and xylometazoline hydrochloride (§ 341.80(d)(2)(vii)(A)(*2*)). The agency is requiring that pediatric products be marketed in a container with a controlled, metered-dose children's safety dropper or spray that is calibrated to deliver no more than a maximum allowable dose. Based on the information on the controlled dropper provided by the comment, which is the manufacturer of the major marketed OTC oxymetazoline pediatric nose drop products, the following doses are being included in this final monograph.

For oxymetazoline hydrochloride, the product must have either a calibrated dropper or a metered-dose spray that delivers no more than 0.027 mg of oxymetazoline hydrochloride per three drops or three sprays. The directions for use are to include the following information: Children 2 to under 6 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril of a 0.025-percent aqueous solution not more often than every 10 to 12 hours. Use only recommended amount. Do not exceed 2 doses in any 24-hour period. [previous two sentences in boldface type] Children under 2 years of age: consult a doctor.

For xylometazoline hydrochloride, the product must have either a calibrated dropper or metered-dose spray that delivers no more than 0.054 mg of xylometazoline hydrochloride per three drops or three sprays. The directions for use are to include the following information: Children 2 to under 6 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril of a 0.05-percent aqueous solution not more often than every 8 to 10 hours. Use only recommended amount. Do not exceed 3 doses in any 24-hour period. [previous two sentences in boldface type] Children under 2 years of age: consult a doctor.

Phenylephrine 0.125 percent aqueous solution is the only other OTC topical nasal decongestant labeled for use by children 2 to under 6 years of age. The agency believes that products containing this drug should also have a calibrated dropper or a metered-dose spray. Using the same standard as above, the product must have either a calibrated dropper or metered-dose spray that delivers no more than 0.135 mg per three drops or three sprays. Similarly, the directions for use are to include the following statement: "Use only recommended amount."

If manufacturers have information that demonstrates that an amount of drug different than those listed above for three drops or sprays of oxymetazoline hydrochloride, xylometazoline hydrochloride, and phenylephrine hydrochloride, the agency will evaluate that information and determine if the above standards should be changed. Manufacturers should submit the information in a citizen petition in accord with § 10.30 (21 CFR 10.30).

References

(1) Department of Health and Human Services, Food and Drug Administration, "Spontaneous Reporting System, Line Listing of Adverse Reports," 1969–1993.

(2) Department of Health and Human Services, Food and Drug Administration, "Spontaneous Reporting System, Line Listing of Adverse Reports," 1970–1993.

(3) Biesalski, P., and K. Marquart, "Therapeutic Aspects of Rhinitis in Early Childhood, Thermoelectrode Investigations with Nasal Decongestants" ("Zur Behandlungder Rhinitis im fruhen Kindesalter. Thermoelektrische Untersuchungen an abschwellenden Nasenmittein") (English Translation), *Schweizerische Medizinische Wochenschrift*, 89(19):510–512, 1959.

(4) "The United States Pharmacopeia XXII—The National Formulary XVII," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 1684, 1989.

9. One comment requested that the status of phenylephrine bitartrate be clarified in the final monograph. The comment stated that data were submitted to the Cough-Cold Panel indicating that phenylephrine bitartrate, while not as commonly used as the hydrochloride salt of phenylephrine, had the same characteristics (Refs. 1 and 2). The comment noted that the proposed dose of phenylephrine hydrochloride in adults is 10 mg which is equivalent to approximately 15.5 mg of phenylephrine bitartrate. Stating that the noninclusion of phenylephrine bitartrate in the Cough-Cold Panel's

report and the tentative final monograph appeared to be an inadvertent omission, the comment requested that phenylephrine bitartrate be classified as a Category I oral nasal decongestant.

The agency acknowledges that phenylephrine bitartrate was submitted as an oral nasal decongestant active ingredient in an effervescent combination cold tablet for OTC use containing 7.8 mg phenylephrine bitartrate (4.1 mg phenylephrine base) which is present in the same amount in solution for oral use. The maximum recommended dose is 8 tablets in 24 hours. Therefore, the maximum dose of phenylephrine bitartrate would be 62.4 mg (32.8 mg phenylephrine base) per day (Ref. 1). However, the ingredient apparently was not reviewed by the Cough-Cold Panel or included in its report, or addressed in the tentative final monograph for OTC nasal decongestant drug products. The agency has reviewed the submitted data and notes that the submission (Ref. 1) states that the Physicians' Desk Reference, 1972 edition, lists two products containing phenylephrine bitartrate (Ref. 3). The agency has determined that these two products are aerosol inhalation devices which deliver micronized particles of isoproterenol hydrochloride and phenylephrine bitartrate for inhalation by mouth into the bronchial tree. The products have the following indications: (1) Acute bronchial asthma and other allergic states, and (2) chronic obstructive pulmonary diseases such as chronic bronchitis and pulmonary emphysema (Ref. 3).

The submission also includes an acute oral toxicity study conducted on phenylephrine bitartrate, chlorpheniramine maleate, and phenylephrine hydrochloride as individual active ingredients. The acute oral LD_{50} for phenylephrine bitartrate alone is presented as 170.7 ± 17.0 mg per kilogram (kg); that for phenylephrine hydrochloride alone is presented as 61.3 ± 11.6 mg/kg (Refs. 1 and 2). In addition, the submission includes a bioavailability (blood level) study of phenylephrine bitartrate combined in an effervescent cold tablet with aspirin and chlorpheniramine maleate (Ref. 2). The study compares phenylephrine plasma levels obtained for three combination drug products containing the following active ingredients: (1) Aspirin, phenylephrine bitartrate (7.1 mg), and chlorpheniramine maleate, (2) aspirin, phenylephrine hydrochloride (5 mg), phenindamine tartrate, and caffeine, and (3) phenylephrine hydrochloride (20 mg) and chlorpheniramine maleate. Although comparable plasma levels of phenylephrine were obtained with the first and second test formulations, the agency has determined that these bioavailability studies do not demonstrate effectiveness because the claimed pharmacological effectiveness of OTC drug monograph active ingredients must be established by controlled clinical investigations (21 CFR 330.10(a)(4)(ii)). No clinical data were submitted to show the effectiveness of phenylephrine bitartrate as an oral nasal decongestant. Moreover, the agency has conducted an extensive literature search and is unaware of any data or information in the scientific literature regarding the use of phenylephrine bitartrate as an oral nasal decongestant active ingredient. The products containing phenylephrine bitartrate that were cited by the comment (Refs. 1 and 3) are aerosol products administered by inhalation and are not indicated for nasal decongestant use. Further, the submitted product has been reformulated and no longer contains phenylephrine bitartrate (Ref. 4). The agency concludes that the data are inadequate to generally recognize phenylephrine bitartrate as safe and effective as an oral nasal decongestant, and this ingredient is not being included in the final monograph for OTC nasal decongestant drug products.

References

(1) OTC Vol. 040192.
(2) OTC Vol. 040193.
(3) "Physicians' Desk Reference—1972," 26th ed., Medical Economics, Inc., Oradell, NJ, pp. 1102 and 1105, 1972.
(4) Letter from B.S. Shuster, Miles Laboratories, Inc., to G. Kerner, FDA, dated April 24, 1987, in OTC Vol. 04NFM, Docket No. 76N–052N, Dockets Management Branch.

10. One comment requested that a product containing phenol 1.56 percent, thymol, sodium perborate, methyl salicylate, alum powder, sage, and honey, used as a spray, atomizer, swab, or gargle, be considered in the nasal decongestant drug products rulemaking. The labeling claim for the product is for "hygienic care of * * * nasal passages" (Ref. 1). In a followup communication with the agency, the comment clarified that phenol is the only active ingredient in the product (Ref. 2).

No data on the use of 1.5 percent phenol for "hygienic care of nasal passages" were submitted to the Cough-Cold Panel following the "call-for-data" notice that was published in the **Federal Register** of August 9, 1972 (37 FR 16029), requesting data on any active ingredients in OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products. Nor were any data on phenol for this use submitted to the agency for inclusion in the tentative final monograph for OTC nasal decongestant drug products published in the **Federal Register** of January 15, 1985 (50 FR 2220). Thus, neither the Cough-Cold Panel in its report (41 FR 38312), nor the agency in its tentative final monograph, considered this ingredient or claim for topically applied nasal drugs in the rulemaking for OTC nasal decongestant drug products. The comment did not submit any data to demonstrate the safety and effectiveness of the claimed active ingredient, phenol, in the nasal passages or to substantiate the claim it requested for this ingredient. Nevertheless, the agency has evaluated the claim "hygienic care of nasal passages" and considers this claim to be vague and meaningless because it does not describe any therapeutic benefits to be obtained from use of the product. Thus, the agency concludes that phenol as an active ingredient and labeling for its use "for hygienic care of nasal passages" are nonmonograph conditions.

References

(1) OTC Vol. 160233.
(2) Telephone communications between A. Horn, co-owner of marketing rights for Formula U, and M. Benson, FDA, March 21 and March 30, 1984, in OTC Vol. 04NFM, Docket No. 76N–052N, Dockets Management Branch.

D. Comments on Dosages for OTC Nasal Decongestant Active Ingredients

11. In response to the agency's proposal (50 FR 2220 at 2229 to 2230) that pseudoephedrine preparations be available at dosage levels twice those previously permitted for OTC use, i.e., 60 mg instead of 30 mg, one comment expressed a hope that pseudoephedrine would continue to be available in 30 mg tablet strength, or if in 60 mg strength, that tablets will be scored for breaking.

The final monograph does not address tablet characteristics such as shape, size, scoring, etc. However, manufacturers must provide consumers with dosage forms and strengths that are consistent with the dosages and directions for use in OTC drug monographs. The adult dosage for products containing pseudoephedrine is 60 mg every 4 to 6 hours. Manufacturers may market a 60-mg product with a one-tablet dosage or a 30-mg product with a two-tablet dosage. The pseudoephedrine dosage for children 6 to under 12 years of age is 30 mg every 4 to 6 hours. Thus, it is reasonable to expect that 30 mg tablets of pseudoephedrine will continue to be available.

12. Several comments recommended that the agency consider new weight-based/age-related pediatric dosing schedules for cough-cold drug products (including nasal decongestants) based on a pediatric dosing unit (PDU) concept that provides for additional age groupings developed to better meet the needs of the growing pediatric patient. Some comments suggested that the Cough-Cold Panel's recommended pediatric dosing schedule of 6 to under 12 years and 2 to under 6 years be replaced with the PDU concept that would utilize a pediatric dosage schedule equivalent to 1/8 the adult dose and include additional age breaks (i.e., 2–3, 4–5, 6–8, 9–10, and 11 years) and/or weight groupings (i.e., 24–35, 36–47, 48–59, 60–71, and 72–95 pounds). Other comments also recommended that this new pediatric dosing schedule be optional. For products targeted primarily for adults, which also incorporate some dosage recommendations for pediatric use, the comments felt that it was reasonable to continue to use the dosing schedule proposed in the tentative final monograph. But for products primarily intended for pediatric use, the comments felt that there was a need for incremental dosing throughout the entire pediatric (under 12 years) age range consistent with the incremental age and weight ranges within the typical growth patterns in children. Stating that the pediatric dosage of cough-cold drug products should be reconciled with the dosage schedules recommended by the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products (Internal Analgesic Panel) (42 FR 35346 at 35489 to 35491, July 8, 1977, which includes additional age groupings), two comments contended that such a change would provide consistency between the various monographs and allow for consistency in the formulation of combination drug products containing a nasal decongestant and an analgesic-antipyretic.

Two comments also recommended that the agency add a professional dosing schedule for children under 2 years of age, based on the PDU concept. As an example, one comment suggested that the professional labeling section for oral pseudoephedrine be amended to include the following: Children 1 year of age, 11.25 mg every 4 to 6 hours, not to exceed 45 mg in 24 hours; children 4 months to under 1 year, 7.5 mg every 4 to 6 hours, not to exceed 30 mg in 24 hours.

Because a number of OTC drug rulemakings could be affected if pediatric dosages are revised as requested by the comments, the agency has published a separate document in the **Federal Register** that discusses pediatric dosages for OTC drug products. Therefore, comments regarding a weight-based, age-related pediatric dosage schedule for pseudoephedrine and other oral nasal decongestants are being deferred at this time and have been addressed in a separate notice entitled "Pediatric Dosing Information for OTC Human Drugs; Intent and Request for Information," published in the **Federal Register** on June 20, 1988 (53 FR 23180). Should pediatric dosage schedules, in general, be revised in the future, the final monograph for OTC nasal decongestant drug products will be amended accordingly.

E. Comments on Labeling of OTC Nasal Decongestant Drug Products

13. Two comments stated that FDA lacks statutory authority to prescribe exclusive lists of terms from which indications for use for OTC drug products must be drawn and to prohibit alternative labeling terminology which is truthful, accurate, not misleading, and intelligible to the consumer. One comment recommended that, instead of prohibiting the use of alternative truthful terminology, FDA should permit manufacturers to choose consumer oriented language to communicate the desired label indications, so long as such language is not false or misleading. Both comments noted that FDA had proposed certain revisions to the "Exclusivity Policy" on April 22, 1985 (50 FR 15810) and stated that they would be submitting further comments on that proposal.

In the **Federal Register** of May 1, 1986 (51 FR 16258), the agency published a final rule changing its labeling policy for stating the indications for use of OTC drug products. Under 21 CFR 330.1(c)(2), the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either: (1) The specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "approved uses"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "approved uses"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "approved uses," plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All OTC drug labeling required by a monograph or other regulation (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under the OTC drug monograph or other regulation where exact language has been established and identified by quotation marks, e.g., 21 CFR 201.63 or 330.1(g).

In the tentative final monograph for OTC nasal decongestant drug products (50 FR 2220 at 2238), supplemental language relating to indications had been proposed and captioned as "Other allowable indications." Under FDA's revised labeling policy (51 FR 16258), such statements are included at the tentative final stage as examples of other truthful and nonmisleading language that would be allowed elsewhere in the labeling. In accordance with the revised labeling policy, such statements would not be included in a final monograph. However, the agency has decided that, because these additional terms have been reviewed by FDA, they should be incorporated, wherever possible, in final OTC drug monographs under the heading "Indications" as part of the indications developed under that monograph. (See comment 16 in section I.E. of this document.)

14. Four comments requested that § 341.80(b) of the tentative final monograph be amended to allow manufacturers to choose from among any of three basic indications provided, i.e., the common cold (cold), allergy, or sinusitis. The comments contended that the intended target populations for products promoted and marketed for treating the common cold, allergy, and sinusitis are different and that specific products should be allowed to be designed or positioned for specific consumer populations. One comment pointed out that the use of all three indications for all products containing oral nasal decongestants, as proposed in § 341.80(b), may not only be extraneous, but potentially confusing to consumers. Two comments provided examples of how this labeling could be extraneous: (1) Indications for hay fever or allergic rhinitis would be inappropriate on a product marketed as a "cold" product, and (2) indications for a cold would be inappropriate for persons suffering from allergy or sinusitis. One comment added that small packages of multi-ingredient combination products contain little label space for necessary indications and warnings. It is therefore important for the distributor of a product to have the option to eliminate indications which are not applicable to a particular segment of the market for which the product is positioned.

The comments requested, therefore, that the indications in § 341.80(b) be amended to allow manufacturers to choose from among any of the basic indications (i.e., the common cold (cold), allergy, or sinusitis) that are appropriate for the consumer market segment to which the product is directed. One comment suggested that § 341.80(b)(1) be modified to read as follows:

> The labeling of the product contains a statement of the indications under the heading "Indications" which includes one or more of the following indications: "For the temporary relief of nasal congestion due to" (select one of the following) "the common cold (cold)," "hay fever (allergic rhinitis)," or "associated with sinusitis."

The agency agrees with the comments that manufacturers should be allowed to choose from among any of the indications proposed for nasal decongestant drug products in § 341.80(b)(1) that are consistent with the intended use of the product.

Thus, in this final monograph the agency is revising the "Indications" in § 341.80(b)(1), to read as follows: (Select one of the following: "For the temporary relief of nasal congestion" or "Temporarily relieves nasal congestion") (which may be followed by any of the following in (i), (ii), and (iii) below):

(i) "due to" (select one of the following: "the common cold" or "a cold").

(ii) "due to" (select one of the following: "hay fever," "hay fever (allergic rhinitis)," "hay fever or other upper respiratory allergies," or "hay fever or other upper respiratory allergies (allergic rhinitis)").

(iii) "associated with sinusitis."

15. With regard to the indications proposed in § 341.80(b), two comments stated that the phrases "for the temporary relief of" and "temporarily relieves" are similar and should be interchangeable.

The agency agrees with the comments that the phrases are interchangeable. Therefore, the agency has included the option of using either phrase in the indications included in § 341.80(b) of this final monograph. (See comments 14 and 16 in section I.E. of this document.)

16. One comment requested that the "other allowable indications" proposed in § 341.80(b)(2) of the tentative final monograph be alternative statements rather than additional statements to the indications proposed in § 341.80(b)(1). The comment contended that this would permit meaningful alternate "consumer oriented" label indications. Another comment assumed that the "other allowable indications" proposed in § 341.80(b)(2) may be identified on product labels as "other indications" if they are separate from the indications identified in § 341.80(b)(1) and are not given greater prominence.

In this final monograph, the agency is revising the indications in § 341.80(b)(1) to allow manufacturers the option of using one or more of the indications (see comment 14 in section I.E. of this document.) The agency considers the required indication statement(s) essential in providing adequate and informative labeling to the consumer. Under the agency's revised labeling policy for OTC drug products, discussed in comment 13 in section I.E. of this document, the "other allowable indications" that were proposed in § 341.80(b)(2) of the tentative final monograph have been included in the final monograph as part of the indications in § 341.80(b). However, the agency does not consider the text of these "other allowable" indication statements as providing complete information that is comparable to the information contained in § 341.80(b)(1). Because they provide additional, complementary information, the previous "other allowable" indications are included in § 341.80(b)(2) of the final monograph as statements that may appear in the "APPROVED USES" boxed area in the labeling, in addition to one or more of the indications in § 341.80(b)(1).

Therefore, the labeling of the product may contain any (one or more) of the following statements, which appear in § 341.80(b)(2) of this final monograph, provided the required information identified in § 341.80(b)(1) (see comment 14 in section I.E. of this document) is also included:

(i) (Select one of the following: "For the temporary relief of" or "Temporarily relieves") (select one of the following: "stuffy nose," "stopped up nose," "nasal stuffiness," or "clogged up nose.")

(ii) (Select one of the following: "Reduces swelling of," "Decongests," or "Helps clear") "nasal passages; shrinks swollen membranes."

(iii) "Temporarily restores freer breathing through the nose."

(iv) "Helps decongest sinus openings and passages; temporarily relieves sinus congestion and pressure."

(v) "Promotes nasal and/or sinus drainage; temporarily relieves sinus congestion and pressure."

(See also comment 17 in section I.E. of this document.)

17. One comment requested modification of the "other allowable indications" for nasal decongestant drug products in proposed § 341.80(b)(2)(i) to include the terms "stuffed-up head" and "stuffy head" as follows: "For the temporary relief of (select one of the following): stuffy nose, stopped-up nose, nasal stuffiness, clogged-up nose, stuffed-up head, stuffy head."

The agency does not consider the terms "stuffed-up head" and "stuffy head" specific enough to be included in this final monograph. The agency believes that other terms could be used in the indication statements to provide more specific information to consumers about the action of this type of drug product than the comment's suggestion of the general terms "stuffed up head" and "stuffy head." In the tentative final monograph, the agency included "relieves sinus pressure" as a Category I indication for nasal decongestants (50 FR 2220 at 2231). Sinus pressure and sinus congestion are closely associated and if congestion is relieved, pressure also would be relieved (50 FR 2220 at 2232). Therefore, in this final monograph, the agency is including the term "sinus congestion" in the indications in § 341.80(b)(2)(iv) and (b)(2)(v). The agency concludes that the terms "sinus congestion" and "sinus pressure" provide more specific information than the comment's suggested terms. In addition, the agency is including these terms in § 341.80(b)(2)(iv) and (b)(2)(v) because those paragraphs primarily deal with "sinus" conditions, whereas the indication in § 341.80(b)(2)(i) primarily deals with "nose" conditions. (See comment 16 in section I.E. of this document for additional discussion of the other indications included in this final monograph.)

However, as discussed in comment 13 in section I.E. of this document, the agency has revised its labeling policy for OTC drug products. FDA has found that it simply is not practical—in terms of time, resources, and other considerations—to set standards for all labeling found in OTC drug products. Accordingly, OTC drug monographs directly address only those labeling items that are related in a significant way to the safe and effective use of covered products by lay persons. These labeling items are the product statement of identity; names of active ingredients; indications for use; directions for use; warnings against unsafe use, side effects, and adverse reactions; and claims concerning mechanism of drug action. Truthful and nonmisleading terms that provide additional information about an OTC drug product but are not directly related to its safe and effective use are considered outside the scope of the OTC drug review and may appear elsewhere in the labeling,

separate from the monograph approved statements. Thus, because consumers are familiar with and use terms such as "stuffed-up head" and "stuffy head," the agency considers these terms as acceptable to be included elsewhere in the labeling (but such terms may not be intermixed with any portion of the labeling required by the monograph and may not detract from such required information). Terms outside the scope of the review will be evaluated by the agency on a product-by-product basis, under the provision of section 502 of the act relating to labeling that is false or misleading.

18. One comment requested that the indication, "helps (select one of the following: relieve, alleviate, decrease, reduce) post-nasal drip" be added as an additional consumer claim for nasal decongestant drug products.

The Cough-Cold Panel placed a similar claim, "checking post-nasal drip," in Category III because such claims are unsubstantiated for nasal decongestants unless studies specifically designed to assess "post-nasal drip" are presented. The Cough-Cold Panel stated in 41 FR 38415 that studies of nasal decongestants have assessed the effect of nasal airway resistance or the ease of breathing but not the effect on rhinorrhea that causes post-nasal drip. The comment did not submit any data concerning the effect of nasal decongestants on rhinorrhea that would support a claim for "post-nasal drip."

Further, the agency is unaware of any data to support consumer recognition of an indication regarding post-nasal drip. The agency reviewed information submitted to the antihistamine final monograph rulemaking requesting an indication for "post- nasal drip." The comment asserted that substantial numbers of consumers recognize that relief of "post-nasal drip" is a desirable end benefit and that consumers clearly understand the term "post-nasal drip." The comment provided two consumer mail panel studies, which were designed to investigate consumer attitudes towards, and usage of, sinus and hay fever remedies. The comment stated that of the 263 responding sinus sufferers, 49 percent (129) considered relief of post-nasal drip important when choosing a sinus remedy. Similarly, 48 percent (119) of the 248 hay fever respondents indicated that relief of post nasal drip was important when choosing a hay fever product. The agency's review of the studies disclosed that they were not designed to demonstrate the effectiveness of OTC antihistamine drug products in relieving the symptom "post-nasal drip" or provide a basis for a "post-nasal drip" indication. These data, therefore, are not useful in supporting a "post-nasal drip" indication for nasal decongestant or antihistamine drug products.

Clinical studies specifically designed to demonstrate the effectiveness of nasal decongestants in relieving "post-nasal drip" would be necessary before this claim could be used in the labeling of any nasal decongestant drug product. Such studies should be designed to evaluate the symptom of "post-nasal drip" in terms of specific symptoms that can be recognized by consumers as "post-nasal drip." The agency suggests that any party interested in studying the use of a nasal decongestant for this claim meet with the agency to discuss an appropriate protocol before beginning the study. For the above reasons, indications pertaining to "post-nasal drip" are not being included in this final monograph for OTC nasal decongestant drug products.

19. Two comments stated that the agency should differentiate between "Warnings" and "Cautions" in OTC drug labeling, and one comment objected to the proposed elimination of the term "Caution(s)" in the labeling of OTC drug products. The comments contended that "Warnings" are harsher (stronger) and more serious than "Cautions" and even preclude use of a product under certain conditions. One comment stated that a "Caution," on the other hand, does not preclude use unless something occurs during use, but it often alerts the consumer to a potential problem. The comment added that a caution may also address a monitoring function to be performed while the product is in use. The second comment stated that a caution should be used to convey important information related to the safe and effective use of the product, but allow for judgment on the part of the user, e.g., "This product may cause drowsiness." The comment felt that the importance of the "Warnings" section was undermined if it contains too much information or if it includes less than serious language. The comment provided several examples of the differences between warnings and cautions and suggested that the agency also consider the term "precautions."

Section 502(f)(2) of the act states, in part, that any drug marketed OTC must bear in labeling "* * * such adequate warnings * * * as are necessary for the protection of users * * *." Section 330.10(a)(4)(v) of the OTC drug regulations provides that labeling of OTC drug products should include "* * * warnings against unsafe use, side effects, and adverse reactions * * *."

The agency notes that historically there has not been consistent usage of the signal words "warning" and "caution" in OTC drug labeling. For example, in §§ 369.20 and 369.21 (21 CFR 369.20 and 369.21), which list "warning" and "caution" statements for drugs, the signal words "warning" and "caution" are both used. In some instances, either of these signal words is used to convey the same or similar precautionary information. In addition, the term "precaution(s)," as in "Drug Interaction Precaution(s)" is often used in OTC drug monographs, but is listed under "Warnings" as, for example, in the rulemakings for OTC nasal decongestant drug products and OTC bronchodilator drug products. (See the Federal Register of January 15, 1985 (50 FR 2220 at 2239) and October 2, 1986 (51 FR 35326 at 35339), respectively.)

FDA has considered which of these signal words would be most likely to attract consumers' attention to that information describing conditions under which the drug product should not be used or its use should be discontinued. The agency concludes that the signal word "warning" is more likely to flag potential dangers so that consumers will read the information being conveyed. The agency is not convinced that consumers will make the distinctions between "warnings" and "cautions" that the comments have made. Further, the agency does not believe that the importance of the "Warnings" section will be undermined if all of the information about unsafe use, side effects, and adverse reactions is presented under a single heading. Therefore, FDA has determined that the signal word "warning," rather than the word "caution," will be used routinely in OTC drug labeling that is intended to alert consumers to potential safety problems. However, except in instances where the agency has stated that a particular warning statement must appear as the first warning after the "Warnings" heading, the agency has no objections if manufacturers list the various warnings statements in their order of preference, e.g., listing first those they consider more serious followed by those they consider to be less serious statements. Drug interaction precaution information will continue to be listed under the heading "Drug Interaction Precautions" as part of the warnings information.

20. One comment stated that it is difficult to read labels of nasal decongestant drug products because the containers are small and the print on the labels also is small. The comment was particularly concerned that the required warnings would not be legible and

recommended that the warnings should be "clearly, in sizable print, be evident, but only a minimum amount." The comment stated that it would be more useful if "warning sheets" or booklets were available with nasal decongestant packages. A second comment requested larger print size and more prominent location of warnings on nasal decongestant products.

In the tentative final monograph for OTC nasal decongestant drug products (50 FR 2220), the agency simplified or revised several and deleted some of the warnings recommended by the Cough-Cold Panel. (See comments 13, 21, 24, 26, 28, and 29 in the tentative final monograph.) The agency believes that the labeling proposed in this final monograph includes only essential information that is necessary to assure proper and safe use of OTC nasal decongestant drug products by consumers. Moreover, the labeling of drugs must comply with section 502(c) of the act which states that a drug shall be deemed to be misbranded:

> If any word, statement, or other information required by or under authority of this Act to appear on the label or labeling is not prominently placed thereon with such conspicuousness (as compared with other words, statements, designs, or devices, in the labeling) and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use.

In general, a product container label needs to bear the following information: A statement of ingredients (section 502(e) of the act), name and address of the manufacturer, repacker, or distributor (section 502(b)(1) of the act), a net contents statement (section 502(b)(2) of the act), a lot number (21 CFR 201.18), and an expiration date (21 CFR 201.17). In some situations, other labeling information is required to appear on the immediate container labeling, e.g., the Reye syndrome warning for drug products containing salicylates (21 CFR 201.314).

When an OTC drug product is packaged in a container that is too small to contain all the required labeling, the agency recommends that the product be enclosed in a carton or be accompanied by a package insert or booklet that contains the information complying with the monograph. Manufacturers are also encouraged to print a statement on the product container label, carton, or package insert suggesting that the consumer retain the carton or package insert for complete information about the use of the product when all the required labeling does not appear on the product container label. Manufacturers who use supplemental labeling should be able to readily provide all labeling information in a larger print size than if all of the labeling is presented on the immediate container. Further, the agency is aware that many manufacturers use bold lettering and a colored label to emphasize certain labeling information, including warnings, on the immediate container and in package inserts. All manufacturers are encouraged to use these as appropriate to highlight and emphasize certain labeling information for the consumers. The agency previously published a request for public comment (56 FR 9363 to 9365, March 6, 1991) on the issue of print size and style of labeling for OTC drug products, and will evaluate comments received before making a final decision on the feasibility of establishing a Federal regulation pertaining to print size and style of OTC labeling.

The Nonprescription Drug Manufacturers Association (NDMA) has recently promulgated guidelines for industry to consider when examining product labels for readability and legibility (Ref. 1). These guidelines are designed to assist manufacturers in making the labels of OTC drug products as legible as possible. The agency commends this voluntary effort and urges all OTC drug manufacturers to examine their product labels for legibility.

Reference

(1) "Label Readability Guidelines," The Nonprescription Drug Manufacturers Association, Washington, copy included in OTC Vol. 04NFM, Docket No. 76N–052N, Dockets Management Branch.

21. Two comments pointed out that the warning for oral nasal decongestants in proposed § 341.80(c)(1)(i)(*b*) (which states: "Do not take this product for more than 7 days. If symptoms do not improve or are accompanied by fever, consult a doctor.") and a similar warning for children in § 341.80(c)(1)(ii)(*b*), could be read to warn against the use of Category I OTC oral nasal decongestant drug products without first consulting a doctor if a fever is present initially. The comments stated that in the advance notice of proposed rulemaking for OTC internal analgesic-antipyretic drug products, the Internal Analgesic Panel classified as Category I the combinations of one or two Category I analgesic-antipyretic active ingredients "* * * with generally recognized as safe and effective nasal decongestant active ingredient(s) provided the product is labeled for the concurrent symptoms involved, * * * for the reduction of fever, * * * " (42 FR 35370, July 8, 1977). One comment contended that while the proposed warning may have limited significance for single ingredient nasal decongestant drug products, it would have a serious and unwarranted adverse effect on the use of combination drug products containing a nasal decongestant along with an analgesic-antipyretic. The comment urged that the proposed warning be reworded to explicitly permit use of a combination product containing an oral nasal decongestant and an antipyretic agent(s) when concurrent symptoms of nasal congestion and fever are present.

The second comment stated that billions of doses of oral nasal decongestants have been used OTC for many years without such a label warning. The comment added that it was unaware of any safety problems that have occurred as a direct consequence of a consumer using a nasal decongestant in the presence of minor fever of short duration, which is the case in the vast majority of instances in which fever is present. On the other hand, the comment contended, the presence of high fever is of importance to the well-being of the consumer, and a doctor should be consulted if such occurs. The comment requested that the above-referenced warnings be amended to read: "(*b*) If symptoms do not improve in 7 days or are accompanied by high fever, consult a doctor."

The comment also stated that some allergic episodes (and even colds) occasionally continue for more than 7 days, particularly in humid climates or in periods of high pollen counts. Therefore, an absolute 7-day use limitation may not always be appropriate. Moreover, the comment stated that its amended warning would be equally informative to consumers who may be taking an oral nasal decongestant product without an antipyretic ingredient as well as to those who may take a combination which includes antipyretic ingredient(s). Thus, the comment requested that this amended warning be included in the following final monographs: (1) OTC nasal decongestant drug products; (2) OTC internal analgesic-antipyretic drug products; and (3) OTC cough-cold combination drug products.

The Cough-Cold Panel noted that a slight fever may be present with the common cold (41 FR 38312 at 38321). The Internal Analgesic Panel stated that antipyretics (fever reducers) may be safely used for self-medication when fever is due to the common cold or flu (42 FR 35346 at 35351). The warnings in § 341.80(c)(1)(i)(*b*) and (c)(1)(ii)(*b*) are not meant to restrict use of an oral nasal decongestant in the presence of minor

fever of short duration such as that which might be associated with a common cold. The agency agrees that a nasal decongestant can be used in such situations. The intent of the warnings is to alert consumers that the presence of a fever might indicate a more serious condition, such as a secondary bacterial infection, for which a doctor should be consulted. For example, a nasal obstruction accompanying a common cold can result in a middle ear infection (acute otitis media). Usually, the first complaint of a middle ear infection is a persistent, severe earache. Other symptoms, such as fever, nausea, vomiting, and diarrhea may occur in young children (Ref. 1). Pneumonia is also often preceded by an upper respiratory infection. Symptoms include chills, sharp pain in the chest, cough, fever, and headache (Ref. 2). Thus, because the agency believes that it is important for consumers to recognize that all fevers are not insignificant occurrences, the word "fever" as proposed in the tentative final monograph is being retained in this final monograph.

This warning for oral nasal decongestant drug products is consistent with the warning included in the final monographs for single ingredient antitussive drug products and single ingredient expectorant drug products, which states: "* * * If cough persists for more than 1 week, tends to recur, or is accompanied by fever, rash, or persistent headache, consult a doctor." (See §§ 341.74(c)(1) and 341.78(c)(2)). These warnings are not meant to restrict the use of an antitussive or an expectorant in the presence of minor fever of short duration such as that which might be associated with a common cold. However, as with the warning for nasal decongestants, the intent of the warnings is to alert consumers that the presence of a fever might indicate a more serious condition, and a doctor should be consulted.

The agency has previously considered inclusion of the word "high" (in reference to fever) in this warning in the final monograph for OTC antitussive drug products. (See 52 FR 30042 at 30054, August 12, 1987.) In that proceeding, the agency determined that the word "high" would not be included in the warning because it is important for the consumer to recognize the presence of fever regardless of whether the fever is high or low. The agency concludes that this principle is equally applicable to the labeling of OTC nasal decongestant drug products. Therefore, the agency is not adopting the second comment's suggested wording related to the use of the term "high" to describe fever.

The agency agrees with the comment that an absolute 7-day limitation may not always be appropriate for oral nasal decongestant drug products. Further, the final monographs for OTC antitussive and expectorant drug products (21 CFR part 341) do not impose a 7-day use limitation, and the agency concludes that such a limitation is also not necessary for oral nasal decongestant drug products. Therefore, the warnings proposed in § 341.80(c)(1)(i)(*b*) and (c)(1)(ii)(*b*) in the tentative final monograph are revised as follows: "If symptoms do not improve within 7 days or are accompanied by fever, consult a doctor." These warnings appear in § 341.80(c)(1)(i)(B) and (c)(1)(ii)(B) of this final monograph.

With regard to labeling of cough-cold combination drug products for which the labeling in the individual applicable monographs conflicts or is inappropriate, the agency has proposed specific labeling in § 341.85 of the tentative final monograph for OTC cough-cold combination drug products. (See 53 FR 30522 at 30562 to 30564.) The antipyretic ingredient in an oral nasal decongestant-analgesic-antipyretic combination drug product would be used specifically to treat a fever. Normally, the labeling for such a product would contain the appropriate portions of the monograph labeling for nasal decongestant and analgesic-antipyretic ingredients. However, the agency recognized that the warnings for nasal decongestants proposed in § 341.80(c)(1)(i)(*b*) and (c)(1)(ii)(*b*) of the tentative final monograph would be inconsistent with the presence of the analgesic-antipyretic ingredient(s) in the product. Therefore, to eliminate this inconsistency, the agency proposed the following warning for such products labeled for use by adults in the cough-cold combinations tentative final monograph: "Do not take this product for more than 10 days. If symptoms do not improve or are accompanied by fever that lasts for more than 3 days, or if new symptoms occur, consult a doctor." For products labeled for use by children 2 to under 12 years of age, the proposed warning reads as follows: "Do not give this product to children for more than 5 days. If symptoms do not improve or are accompanied by fever that lasts for more than 3 days, or if new symptoms occur, consult a doctor." (See 53 FR 30522 at 30563.) The agency will address this warning in the final monograph for OTC cough-cold combination drug products, in a future issue of the **Federal Register.**

References

(1) Berkow, R., editor, "The Merck Manual," 16th ed., Merck and Co., Rahway, NJ, pp. 2331–2332, 1992.

(2) Berkow, R., editor, "The Merck Manual," 16th ed., Merck and Co., Rahway, NJ, pp. 681–685, 1992.

22. One comment contended that the agency's proposed drug interaction precautions for adults and children in § 341.80(c)(1)(i)(*d*) and § 341.80(c)(1)(ii)(*d*), respectively, essentially duplicate statements required in other warnings. The comment requested that the proposed warning in § 341.80(c)(1)(i)(*c*) be modified to include the "Drug Interaction Precaution" information in § 341.80(c)(1)(i)(*d*) to read as follows: "Do not take this product if you are being treated for heart disease, depression, high blood pressure, thyroid disease, diabetes, or have difficulty in urination due to enlargement of the prostate gland unless directed by a doctor." Likewise, the comment requested that the proposed warning in § 341.80(c)(1)(ii)(*c*) be modified to include the "Drug Interaction Precaution" information in § 341.80(c)(1)(ii)(*d*) to read: "Do not give this product to children who are being treated for heart disease, thyroid disease, diabetes, high blood pressure, or depression unless directed by a doctor." The comment concluded that these revisions would eliminate redundancy in the warnings language.

The agency agrees that the statements are similar but does not agree that drug interaction precautions should be combined with warnings. The agency believes the drug interaction precaution needs to be highlighted in order to adequately inform individuals who may not otherwise be aware of serious (even life-threatening) adverse effects due to potentiation of the adverse effects of one drug by another taken concurrently.

In discussing drug interactions, the Cough-Cold Panel stated that it had recommended appropriate labeling for drug interactions where there are serious concerns (41 FR 38312 at 38335). In the case of nasal decongestants, the Cough-Cold Panel stated that patients taking other drugs (e.g., monoamine oxidase inhibitors whose action can intensify sympathomimetic drug action), should not use oral nasal decongestants except under the advice and supervision of a physician (41 FR 38312 at 38397). The Cough-Cold Panel therefore recommended a specific warning, in the form of a drug interaction precaution, to alert the subgroup of the OTC nasal decongestant target population taking prescription medication for certain

chronic disease conditions, to their special risk in using OTC nasal decongestants concurrently. The Cough-Cold Panel recommended the following drug interaction precaution statement: "Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor except under the advice and supervision of a physician." (See 41 FR 38312 at 38423.) For these reasons, the agency also proposed this drug interaction warning for OTC sympathomimetic amine bronchodilator drugs (41 FR 38312 at 38370 through 38373).

The agency discussed this statement in the tentative final monograph for OTC nasal decongestant drug products (50 FR 2220, January 15, 1985). In response to the Cough-Cold Panel's recommendation, two comments contended that terms such as "antihypertensive," "antidepressant," and "monoamine oxidase inhibitor" (MAOI) are highly technical; that only a small percentage of the population is likely to understand this warning; and that including such a warning in the labeling of an OTC drug is contrary to the well-established principle that unnecessary or confusing precautions tend to dilute the significance of all instructions in the labeling and, hence, should be avoided (50 FR 2220 at 2231). Accordingly, the agency proposed to simplify the precaution statement as follows: "*Drug interaction precaution.* Do not take this product if you are presently taking a prescription drug for high blood pressure or depression, without first consulting your doctor." (See proposed § 341.80(c)(1)(i)(*d*).) Also with the tentative final monograph, the agency proposed to add new § 341.80(c)(1)(ii)(*d*) for children, as follows: "*Drug Interaction Precaution:* Do not give this product to a child who is taking a prescription drug for high blood pressure or depression, without first consulting the child's doctor." The wording for OTC bronchodilator drug products was similarly revised in the tentative final monograph (47 FR 47520 at 47523) and the final monograph (51 FR 35326 at 35338).

After publication of the tentative final monograph for OTC nasal decongestant drug products, the agency became aware of a need to modify the wording of the drug interaction precaution statement. Information was submitted to the agency showing that the antitussive ingredient dextromethorphan interacts with prescription drugs containing MAOI's. Case reports and articles in the literature describe severe reactions, including death, from this combination of drugs. In preparing a proposal to amend the final monograph for OTC antitussive drug products to provide for a new drug interaction precaution for that class of OTC drugs, the agency determined a need to modify the language of the existing precaution statement for OTC bronchodilator and nasal decongestant drugs, largely because of expanded use of MAOI drugs. There is evidence that MAOI drugs are also being used to treat conditions, such as bulimia and panic disorder, that are not readily associated with depression. Further, the newer MAO B inhibitors are being used to treat Parkinson's disease. Finally, the use of MAOI's in hypertension has essentially ceased. In order to have consistent language among the three drug classes, the agency published proposals to amend the antitussive final monograph (57 FR 27666), bronchodilator final monograph (57 FR 27662), and the nasal decongestant tentative final monograph (57 FR 27658) to provide for the following warning:

Drug interaction precaution. Do not use this product if you are taking a prescription drug containing a monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions), without first consulting your doctor. If you are uncertain whether your prescription drug contains an MAOI, consult your doctor before taking this product.

The case reports and literature articles are discussed in detail in the proposed amendment to the final monograph for OTC antitussive drug products (57 FR 27666).

The comments received in response to the proposed amendments are discussed in detail in a final rule for OTC antitussive drug products (58 FR 54232, October 20, 1993) and OTC bronchodilator drug products (58 FR 54238, October 20, 1993). In brief, four comments that suggested modifications to the wording of the drug interaction precaution statement were not adopted, and one comment that suggested a 2-week washout period be included was adopted.

Accordingly, the agency is amending § 341.80(c)(1)(i)(*d*) for OTC nasal decongestant drug products to read:

Drug interaction precaution. Do not use this product if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your prescription drug contains an MAOI, consult a health professional before taking this product.

Also, the agency is amending § 341.80(c)(1)(ii)(*d*) to read:

Drug interaction precaution. Do not give this product to a child who is taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your child's prescription drug contains an MAOI, consult a health professional before giving this product.

23. Three comments contended that the agency should not require the warning for topical nasal decongestants proposed in § 341.80(c)(2)(iii)(*b*) of the tentative final monograph, which reads: "Do not use this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

One comment contended that the warning should not be required because systemic distribution of topical nasal decongestants is minimal. A second comment stated that such a warning is not warranted for topical products containing oxymetazoline. Referring to studies in dogs that compared the doses of oxymetazoline given intranasally and intravenously to elicit a cardiovascular effect (i.e., increase in blood pressure) and that showed substantial differences, the comment indicated that the amount of oxymetazoline required to elicit any systemic effect by the intranasal route would be virtually unachievable with marketed products. Based on the amount of the drug which is required to cause a systemic effect, the comment argued that there is no reason to believe that patients with cardiac problems, diabetes, or hyperthyroidism would be at any greater risk than the general population. In addition, the comment stated that its review of adverse experience files showed no cardiovascular side effect from oxymetazoline that was not associated with significant overuse, either in frequency of use, quantity of use, or both. The comment stated that the agency's proposed warning not to overuse the product deals adequately with risks to patients with cardiac problems, diabetes, or hyperthyroidism and that the additional warning is unnecessary.

The third comment indicated that the proposed warning should be deleted from the monograph because it is conjectural that systemic effects can occur as a result of absorption from the gastrointestinal tract if an excessive amount of topically applied nasal decongestant drug is swallowed. The comment stated that it was unaware of any data that support the position that an excessive amount of drug can be, or

is, swallowed when the product is used as directed. The comment cited numerous studies to support its position (Refs. 1 through 19). In addition, the comment attached a summary of published studies addressing the issue of intranasally-applied decongestants and possible cardiovascular changes (Ref. 20). The summary indicated that oral threshold doses reported to be associated with changes in pulse rate and/or blood pressure are 6 to 10 times higher than the maximal dose of phenylephrine or ephedrine administered intranasally. In the case of phenylephrine hydrochloride, the comment stated that if an entire dose of a 0.5-percent nasal spray, which contains 1.5 mg phenylephrine hydrochloride, were ingested, it would amount to only a small fraction of the Category I recommended oral dose of 10 mg for this drug. In the case of 0.5 percent ephedrine sulfate, a typical adult dose of 0.6 mg would be delivered and, 100 percent of the dose, if ingested, would amount to only a small fraction of the Cough-Cold Panel's recommended oral dose of 8 to 12 mg as a bronchodilator (41 FR 38312 at 38408).

The agency has reviewed the studies cited by one comment as well as other pertinent information concerning the side effects caused by topical nasal decongestants. Based on its review of the available data and information, the agency concludes that the warning—concerning the use of topical nasal decongestants in patients with heart disease, high blood pressure, thyroid disease, and diabetes—as discussed in the tentative final monograph (50 FR 2220 at 2222 to 2223) is appropriate for topical nasal decongestant drug products containing ephedrine or one of its salts, phenylephrine hydrochloride, naphazoline hydrochloride, oxymetazoline hydrochloride, and xylometazoline hydrochloride. The agency does not believe that the studies adequately support the safe use of topical nasal decongestants in patients with heart disease, high blood pressure, thyroid disease, or diabetes without the supervision of a physician. Further, the agency's adverse reaction data indicate that, after rebound congestion, cardiovascular effects are among the most numerous adverse effects reported.

The agency has reviewed its adverse reaction report files (Ref. 21) and finds that cardiovascular effects such as bradycardia, tachycardia, hypertension, and hypotension have been reported for products containing topical nasal decongestants, particularly for oxymetazoline. In most of the cases of cardiovascular effects, the topical nasal decongestant drug was reported to be the only drug used by the patient and was believed to be the suspect drug. Based on these adverse reaction files, the agency is concerned that certain individuals may be more susceptible to developing cardiovascular effects when using topical nasal decongestants. Further, although topical nasal decongestant drugs are recommended for no more than 3 days use, the agency is aware that excessive use of topical nasal decongestants does occur (see comment 2 in section I.A. of this document). Such excessive use could also increase the possibility that individuals with the conditions listed in the warning might develop adverse effects.

The agency does not believe that the studies submitted by one of the comments adequately support the safe use of topical nasal decongestants containing ephedrine or one of its salts, phenylephrine hydrochloride, naphazoline hydrochloride, oxymetazoline hydrochloride, or xylometazoline hydrochloride in patients with heart disease, high blood pressure, thyroid disease, or diabetes without the supervision of a physician. A number of the studies (Refs. 1 through 8) were not useful to evaluate topical effects of the nasal decongestants because the drugs were administered by oral or injectable routes. In 11 of the submitted studies (Refs. 9 through 19), nasal decongestants were administered intranasally in subjects with cardiovascular disorders, diabetes, or thyroid disease. In 1 of the 11 studies (Ref. 19), the number of hypertensive subjects could not be determined. In the remaining 10 studies, 833 subjects were studied but only 50 subjects had the conditions referred to in the warning. Thus, the agency does not consider this limited number of subjects adequate to support deletion of the warning.

The data also show that the oral doses of some topical nasal decongestants that are required to produce adverse reactions exceed the recommended topical dosages; however, none of the submitted data address the extent of absorption of nasal decongestants from the nasal mucosa, and this may be more analogous to intravenous administration than to oral administration of the drug. Many drugs (e.g., sublingual nitroglycerin, nitroglycerin spray, corticosteroids) are absorbed well from the mucosa of the oropharynx and can be more rapidly and completely absorbed than when ingested orally.

Further, the submitted data do not contain sufficient information to exclude the systemic effects alluded to in the warning. Actual data on blood pressure changes were not provided in most of the studies, and the degree of absorption of the drugs from topical intranasal administration was not addressed. Although topical nasal decongestants are administered in smaller doses than the oral doses of these drugs, the safety of these drugs when used without physician supervision by patients with heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland has not been adequately demonstrated.

Based on the above reasons, the agency is retaining the following warning for topical nasal decongestant products containing ephedrine, phenylephrine hydrochloride, naphazoline hydrochloride, oxymetazoline hydrochloride, or xylometazoline hydrochloride that was proposed in the tentative final monograph: "Do not use this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

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(21) Department of Health and Human Services, Food and Drug Administration, "Spontaneous Reporting System, Line Listing of Adverse Reports: Nasal–76–83," 1976–1983, in OTC Vol. 04NFM, Docket No. 76N–052N, Dockets Management Branch.

24. One comment contended that the proposed warnings in § 341.80 for topical nasal decongestant sprays and drops (which state: "Do not use this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor;" "Do not exceed recommended dosage because burning, stinging, sneezing, or increase of nasal discharge may occur;" and "Do not use this product for more than 3 days. If symptoms persist, consult a doctor.") do not apply to its company's "innovative and unique one-way metered pump spray delivery system." The comment explained that the metered delivery system for its topical nasal decongestant drug products substantially reduces dosage variability, assures uniform dosage and spray pattern, and thereby further minimizes any possibility of significant systemic absorption and systemic side effects. For this reason, the comment recommended that for these products the agency eliminate the warning in proposed § 341.80(c)(2)(iii)(*b*) not to use topical nasal decongestants if certain disease conditions are present. Stating that the spray pattern achieved with the pump virtually eliminates the nasal irritation and rebound congestion sometimes associated with conventional sprays and drops and that marketing experience has confirmed the purpose of the pump's design, the comment also contended that the warnings proposed in § 341.80(c)(2)(i)(*a*) and (c)(2)(iii)(*a*) concerning burning, stinging, etc., and a restriction to only 3 days' dosage should not be required for its metered pump products.

The comment did not submit any data to support its contention that the use of a metered pump delivery system makes the above mentioned warnings unnecessary. Furthermore, the agency believes that regardless of the uniformity of the dosage and spray pattern of a topical nasal decongestant, the pharmacologic action of nasal decongestant active ingredients can produce adverse reactions in some susceptible individuals who have heart disease, high blood pressure, diabetes, etc. Thus, in the interest of consumer safety, the warning proposed in § 341.80(c)(2)(iii)(*b*) would still be applicable, regardless of the nasal spray delivery system. Also, a uniform dosage and spray pattern would not eliminate the possibility of overuse of the topical nasal decongestant drug product. An individual might use too much of the spray by repeatedly applying the medication or by using the product longer than the recommended 3 days use. Thus, rebound congestion could occur and the warning in § 341.80(c)(2)(iii)(*a*) would be applicable. The agency is unaware of data to support the comment's contention that a uniform dosage and spray pattern could help to lessen adverse effects such as burning, stinging, sneezing, etc., which might be caused by an excessive dose of a topical nasal decongestant. In the absence of data, the agency cannot agree with the comment that the warning regarding burning, stinging, sneezing in § 341.80(c)(2)(i)(*a*) (redesignated as § 341.80(c)(2)(i)(B) in this final monograph) is unnecessary for its pump spray delivery system. Therefore, the agency concludes that the warnings for topical nasal decongestants mentioned by the comment are applicable regardless of the spray delivery system.

The agency notes that a request of the type submitted by the comment (for deletion of certain warnings for a specific metered pump delivery system) could be considered as a request for an exemption from the monograph requirements or as a request for a monograph deviation. For an exemption, which would require the submission of a petition to amend the final monograph, data would have to be submitted to support the comment's contention that certain warnings are unnecessary for the metered pump spray delivery system. An exemption from these warning statements could then be included in the monograph for all nasal decongestant ingredients marketed in the specified metered dose spray dosage form along with the specifications for the specific metered pump spray delivery system. The agency believes that it would be difficult to write such specifications for inclusion in a monograph and thus considers a monograph deviation to be a more suitable alternative. A monograph deviation is covered by the regulations in 21 CFR 330.11. These regulations provide for the submission of a limited new drug application (NDA) covering only the deviation from the final monograph. Under these regulations, data submitted in support of an NDA for a product that deviates from an OTC drug final monograph must be in the form required by 21 CFR 314.50. Also, the request must include a statement that the product meets all conditions of the applicable OTC drug monograph except for the deviation for which approval is requested. The application may omit all information except that pertinent to the deviation. For the particular product discussed in the comment, the manufacturer should provide sufficient manufacturing control data to assure FDA of the uniformity of the metered dose delivery and of the spray pattern claimed for the drug product, and should include adequate clinical data to confirm that the warnings are unnecessary.

25. One comment recommended that the following statements be allowed for topical nasal decongestants marketed in a one-way metered pump delivery system: "Won't draw back nasal fluids," "unique one-way pump prevents draw-back contamination," "protects against

draw-back contamination," and "unique metered spray delivers a controlled/metered dose." In addition, the comment contended that "accurate" statements such as "long lasting relief" are appropriate for oxymetazoline-containing nasal decongestant drug products.

The agency believes that information describing a metered dose delivery system, such as that recommended by the comment, is product specific and above and beyond the scope of the standards set by this final monograph for OTC nasal decongestant drug products.

The OTC drug review program establishes conditions under which OTC drugs are generally recognized as safe and effective and not misbranded. Two principal conditions determined during the review are allowable ingredients and the allowable labeling for those ingredients. The FDA has determined that it is not practical—in terms of time, resources, and other considerations—to set standards for all labeling found in OTC drug products. Accordingly, OTC drug monographs regulate only labeling related in a significant way to the safe and effective use of drug products by consumers. OTC drug monographs establish the allowable labeling for the following: the product statement of identity; the names of active ingredients; the indications for use; the directions for use; the warnings against unsafe use, side effects, and adverse reactions; and the claims concerning the mechanism of drug action. Accordingly, such information as that recommended by the comment is outside the scope of the OTC drug review.

The agency emphasizes that even though such information is outside the scope of the OTC drug review, it may be used in labeling subject to the prohibitions in section 502 of the act relating to labeling that is false or misleading. Such information will be evaluated by the agency on a case by case basis in conjunction with normal enforcement activities relating to that section of the act. Moreover, any information that is outside the scope of the review, even though it is truthful and not misleading, may not appear in any portion of the labeling required by the monograph and may not detract from such required information.

Regarding the comment's claim of "long lasting relief" for oxymetazoline-containing nasal decongestant drug products, the agency notes that oxymetazoline hydrochloride has a frequency of use of "not more often than every 10 to 12 hours" which is the longest duration of action of any topical nasal decongestant in the monograph. As stated in the tentative final monograph for OTC nasal decongestant drug products, the "duration of effect has been included in the established dosages and directions for these products by stating the frequency of use (in terms of hours), which indirectly tells the consumer the duration of the products' effects" (50 FR 2220 at 2236). Although not included in the monograph, the agency has no objection to a statement such as "long lasting relief" appearing in the labeling of an OTC nasal decongestant drug product containing oxymetazoline hydrochloride. However, as stated above, such statements are subject to the prohibitions in section 502 of the act and may not appear in any portion of the labeling required by the monograph and may not detract from such required information.

26. Two comments suggested that the proposed warning for oral nasal decongestants in § 341.80(c)(1)(i)(*a*) and (c)(1)(ii)(*a*) (which states: "Do not exceed recommended dosage because at higher doses nervousness, dizziness, or sleeplessness may occur.") be revised. One comment suggested revising the warning sections to state: "Do not exceed recommended dosage. If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a physician." This comment stated that, as the warning presently reads, it might suggest to consumers that nervousness, dizziness, and sleeplessness are the only consequences of exceeding the recommended dose, which is not necessarily so. The comment added that "nervousness, dizziness, and sleeplessness are significant enough to be a separate warning as they may, on occasion, occur at the recommended dose." The second comment suggested that the warning sections be rewritten to state: "Do not exceed recommended dosage. If nervousness, dizziness, or sleeplessness occur, consult a doctor." The comment explained that a patient's medical history information is needed before a doctor can appropriately advise the patient whether to continue the same dose, decrease the dose, or discontinue the drug if the above-mentioned symptoms occur.

The agency agrees with the comments that the warnings for oral nasal decongestants proposed in § 341.80(c)(1)(i)(*a*) and (c)(1)(ii)(*a*) of the tentative final monograph could be revised to make them separate statements. Both comments proposed the same first statement, which is the same language as proposed in the tentative final monograph and which the agency is adopting in this final monograph. However, the comments differ in their suggested second statement. The second comment did not state to discontinue use of the drug if the above-mentioned symptoms occur. The agency believes that if nervousness, dizziness, or sleeplessness occur with use of a nasal decongestant drug, it is best to advise the consumer to discontinue use of the drug as a safety measure, and to consult a doctor for advice. In addition, in order to emphasize that the drug should not be overused, the agency is requiring that the first part of the warning appear on the label of the product in boldface type. Therefore, in the final monograph, the warnings read as follows: "Do not exceed recommended dosage. [first sentence in boldface type] If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a doctor."

27. One comment contended that the proposed warning for topical nasal decongestants in § 341.80(c)(2)(i)(*a*) (which states: "Do not exceed recommended dosage because burning, stinging, sneezing, or increase of nasal discharge may occur.") does not appear to be justified on the basis of consumer information and should be deleted from the monograph. The comment stated that one major firm reviewed its consumer complaint file on nasal sprays over a period of 5 years and found an average complaint rate of less than one complaint per million packages sold. The comment added that other firms have reported similar data. The comment questioned the logic of the cause and effect statement contained in the warning as it applies to topical nasal decongestant sprays and drops, i.e., that the reactions of "burning, stinging, sneezing, or increase of nasal discharge" will be the result of exceeding the recommended dosage. The comment argued that even if an excessive amount of spray or drops is used, which seems highly unlikely, the solution will either run out of the nose or drain to the back of the throat or both. In either case, the comment indicated that the amount of liquid that will adhere to the nasal mucosa is relatively constant.

In the tentative final monograph for OTC nasal decongestant drug products, the agency reviewed a related comment regarding the warning "Do not exceed recommended dosage because burning, stinging, sneezing, or increase of nasal discharge may occur." The agency concluded that this warning statement should apply to all topical nasal decongestant active ingredients administered as a drop, spray, jelly, or in an inhalant dosage form. (See 50 FR 2220 at 2232 to 2233.)

The agency also reviewed the labeling of topical nasal decongestant drug products previously approved under NDA's. The NDA labeling for products containing the nasal decongestant active ingredient oxymetazoline contained the statement: "Local stinging and slight burning can occur with any topical nasal decongestant" (Ref. 1). The NDA labeling for a product containing xylometazoline hydrochloride contained the following statement in the "Adverse Reactions" section: "Because of the pharmacological relationship among sympathomimetic nasal decongestants, the following types of effects may occur: burning, stinging, dryness of the nasal mucosa, sneezing; * * *." (Ref. 2). Furthermore, the AMA "Drug Evaluations Annual" describes typical adverse reactions of topical nasal decongestants as temporary discomfort such as stinging, burning, or dryness of the nasal mucosa, while the specific adverse reactions for naphazoline, oxymetazoline, and xylometazoline include sneezing as well (Ref. 3). Thus, the agency concludes that a warning concerning burning, stinging, sneezing, or an increase in nasal discharge is supported by clinical evidence and that the consumer complaint data, as presented by the comment, are inadequate to substantiate deletion of such a warning from the monograph. Based on the NDA labeling and AMA "Drug Evaluations," the agency believes that burning, stinging, sneezing, or an increase in nasal discharge may occur at recommended dosages and has revised the warning into two separate warnings to clarify that these side effects can occur at recommended doses. Therefore, the following revised warnings are being included in the final monograph: "Do not exceed recommended dosage," and "This product may cause temporary discomfort such as burning, stinging, sneezing, or an increase in nasal discharge." Additionally, in order to emphasize that the drug should not be overused, the agency is requiring that the warning "Do not exceed recommended dosage" appear on the label of the product in boldface type.

References

(1) Copy of FDA approved labeling from NDA 14–717, in OTC Vol. 04NFM, Docket No. 76N–052N, Dockets Management Branch.

(2) Copy of FDA approved labeling from NDA 11–919 in OTC Vol. 04NTFM, Docket No. 76N–052N, Dockets Management Branch.

(3) "Drug Evaluations Annual," American Medical Association, Milwaukee, WI, p. 408 and pp. 415–418, 1991.

28. One comment disagreed with the agency's proposed warning for topical nasal decongestant drug products containing 1 percent phenylephrine hydrochloride, which states: "Frequent use of this product may cause nasal congestion to recur or worsen." The comment contended that the data in the two clinical studies (comparing the safety and effectiveness of phenylephrine 1 percent vs. phenylephrine 0.5 percent) that were reviewed by the agency in the tentative final monograph (50 FR 2220 at 2229) were insufficient to warrant the proposed warning. The comment argued that the agency itself admits that "* * * the differences in side effects between the two groups [0.5 percent vs. 1 percent phenylephrine] were not statistically significant" (50 FR 2229). The comment stated that one of the studies, by Jolly et al. (Ref. 1), confirms this view by noting that "The higher incidence of responses which probably reflects rebound hyperemia in the 1-percent group (19 percent) as compared to the 0.5-percent group (4 percent) is of questionable significance from the statistical standpoint." The comment added that Jolly et al. question the reliability of the method used in the study for assessing side effects. In addition, the comment contended that even if one were to assume that the method of data collection on side effects used by Jolly et al. was unquestionable, the two studies are not confirmatory in relation to the "possible" effect seen in the Jolly et al. study. The comment also mentioned that critical information (i.e., the use of prestudy medication and the baseline conditions of individuals who were reported to have experienced the side effect of congestion during drug usage periods) is missing from the assessment of side effects in these studies.

In summary, the comment stated that the two clinical studies were designed to assess efficacy, and the methodology was not sufficiently sensitive to define confidently a comparative safety profile for the two concentrations (0.5 and 1 percent) of phenylephrine. The comment concluded that because the suggestive data form at best a possible link of a side effect and are insufficient to warrant a label warning for products containing 1 percent phenylephrine, the proposed warning should not be included in the final monograph.

The agency disagrees with the comment that the two clinical studies were designed to assess only effectiveness. Information in the manufacturer's comment shows that the two clinical studies were conducted to assess "* * * the relative safety of the two concentrations," and "* * * to compare the tolerance exhibited * * * to (0.5 and 1 percent phenylephrine hydrochloride nose drops) under conditions of exaggerated (i.e., maximum limit of the present recommended dosage) use" (Ref. 2). In reviewing the Jolly et al. study (Ref. 1), the agency observed that:

> Twelve subjects who received the 1-percent concentration and 10 who received the 0.5-percent concentration experienced side effects such as headache, nausea, dizziness, nasal edema, and erythema. The differences in side effects between the two groups were not statistically significant. However, FDA notes that the data did suggest that the 1-percent concentration seemed more likely to induce rebound congestion. The investigator also noted that the 0.5-percent concentration may be slightly better tolerated (Ref. 3).

As discussed by the Cough-Cold Panel in its report, topical nasal decongestants are known to cause rebound congestion with continued frequent use (41 FR 38312 at 38396 to 38403). However, the Cough-Cold Panel felt that the problem could be minimized if topical nasal decongestants are administered in accordance with label directions at recommended intervals for periods not exceeding 3 days (41 FR 38396). Rebound congestion occurs when topical nasal decongestants (i.e., nasal sprays, drops, jellies, and some inhalants) are used too often and for too long a period of time. Prolonged and continued use of topical nasal decongestants causes the nasal mucous membranes to become more congested and swollen as the effect of the drug wears off. The recurrence of congestion causes the user to reapply the drug. Repeated applications of the drug cause the nasal passages to reopen, but only briefly. This effect leads to continued use of the drug and perpetuates the rebound phenomenon. As discussed in comment 2, the agency has concluded that the 3-day use warning does not adequately explain to consumers the problem of rebound congestion. Therefore, the agency is clarifying the 3-day use warning as follows: "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor." These same revisions are being made in the 7-day use warning for l-desoxyephedrine that appears in § 341.80(c)(2)(ii) of this final monograph.

Based on the above discussion, the agency is deleting the specific warning for 1 percent phenylephrine hydrochloride that was proposed in the tentative final monograph in § 341.80(c)(2)(v) and is instead requiring that 1 percent phenylephrine hydrochloride, as well as all other

topical nasal decongestants except l-desoxyephedrine, bear the warning "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor." This warning appears in §§ 341.80 (c)(2)(iii)(A), (c)(2)(v), (c)(2)(viii), and (c)(2)(ix) of this final monograph.

The agency's detailed comments and evaluations of the data are on file in the Dockets Management Branch (Ref. 3).

References

(1) Jolly, E. R. et al., "Comparative Determination of Two Formulations of Neosynephrine," draft of unpublished study, Comment No. C0125, Docket No. 76N–0052, Dockets Management Branch.

(2) Comment No. C0125, Docket No. 76N–0052, Dockets Management Branch.

(3) Letter from W. E. Gilbertson, FDA, to E. J. Hiross, Sterling Drug, Inc., coded LET081, Docket No. 76N–052N, Dockets Management Branch.

29. One comment stated that, to its knowledge, no studies exist which show a definite association between the use of propylhexedrine and the occurrence of rebound congestion. The comment stated that one 2-week study and a single-dose study cited by the Cough-Cold Panel show that rebound congestion is not a problem with propylhexedrine, and a third study was ambiguous and results only "suggest a possible rebound congestion" (41 FR 38312 at 38402). The comment added that there are no studies which conclude that 3 days is the duration of therapy which reduces any risk of rebound congestion, and contended that the agency's proposed 3-day use limitation warning in § 341.80(c)(2)(vi) and (c)(2)(x) is arbitrary and unsubstantiated. The comment recommended that the agency revise proposed § 341.80(c)(2)(vi) and (c)(2)(x) to read: "Not to be used for prolonged periods."

The agency has reevaluated the studies cited by the comment (Refs. 1, 2, and 3). One study by Connell (Ref. 1) involved 64 adults with nasal congestion associated with acute coryza. The study was designed to compare the effect of a propylhexedrine inhaler on nasal airway resistance measured before inhalation to develop baseline data and after inhalation to measure the response pattern. With respect to this study, the Cough-Cold Panel stated that "measurements made 4 hours after the initial inhalation, that is, 2 hours after the repeat inhalation, suggest a possible rebound congestion" (41 FR 38312 at 38402). In a single-dose study by Hamilton (Ref. 2), the nasal decongestant effect of a propylhexedrine inhaler was compared with a placebo inhaler in 50 adult subjects with nasal congestion due to head cold. The subjects were divided equally between active and placebo groups. This study concluded that drug action of the propylhexedrine inhaler compared to placebo was demonstrated and that there were no suggestions of adverse effects. The Cough-Cold Panel had reviewed this study and stated that "no side effects or evidence of rebound congestion was noted" (41 FR 38312 at 38402). Another study by Connell (Ref. 3), which was not discussed by the Cough-Cold Panel, consisted of a comparison between groups of normal volunteers assigned to active and placebo inhalers (20 active and 10 placebo). Subjects were instructed to use a dose of two inhalations per nostril every 4 hours during the waking hours for a 2-week period. The study concluded that there were no signs of "rebound congestion" in the 20 normal volunteers who used the propylhexedrine inhaler every 4 hours for 2 weeks.

The agency agrees with the Cough-Cold Panel that the first study by Connell (Ref. 1) does suggest rebound congestion. In addition, although no rebound was seen with the single-dose study performed by Hamilton (Ref. 2), this is not sufficient proof that rebound does not occur because rebound is more likely to occur with repeated doses. The second study by Connell (Ref. 3) was intended to measure rebound after use of the propylhexedrine inhaler. Although the study concluded that there were no signs of rebound in 20 normal volunteers, the agency believes it would have been more meaningful if the study had included a number of subjects with nasal congestion associated with head colds or acute coryza as well as some subjects who used the recommended dose of two inhalations every 2 hours for a number of days. Thus, the agency believes that the second Connell study (Ref. 3) does not establish that rebound congestion due to propylhexedrine inhalation under actual use conditions does not occur.

Other references indicate that sympathomimetic amines can cause rebound congestion (Refs. 4 and 5). For example, one source notes that side effects of propylhexedrine include rebound congestion, headache, and, in rare instances, an increase in blood pressure (Ref. 4). Another source states that a major limitation of therapy with nasal decongestants is that loss in efficacy and "rebound" hyperemia and worsening of symptoms often occur with chronic use or when the drug is stopped (Ref. 5).

Regarding the comment's contention that the 3-day use limitation warning is arbitrary and unsubstantiated, the agency concluded in the tentative final monograph that the 3-day warning is justified in view of the Cough-Cold Panel's finding "that nasal decongestants can produce rebound congestion after a short period of use," i.e., 4 to 6 hours; as well as by prolonged use caused by habitual use for varying periods of time (50 FR 2232). Moreover, the agency finds the comment's suggested warning "Not to be used for prolonged periods" to be too vague and indefinite. Because some individuals have a tendency to use topical nasal decongestants for prolonged periods, the agency believes that it is important to specifically state how long the product should be used. Because rebound congestion can occur after a short period of use, the agency believes that a 3-day use limitation provides a reasonable period of time for relief of nasal congestion as well as an adequate margin of safety against the development of rebound congestion. Thus, the comment's recommendation is not being accepted.

The agency has determined that it is important to inform consumers of the consequences of too frequent or prolonged use of propylhexedrine or other topical nasal decongestants. Such products will have to bear the following warning: "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor." (See also comment 2 in section I.A. of this document and comment 28 in section I.E. of this document.)

References

(1) Connell, J., "Analysis of Study Designed to Characterize 'Benzedrex' Inhaler Response with Nasal Airway Resistance Measurements and Nasal Congestion Ratings," draft of unpublished study, in OTC Vol. 040253.

(2) Hamilton, L., "Analysis of Study Designed to Characterize Propylhexedrine Inhaler Activity as Measured by Nasal Airway Resistance and Nasal Congestion Criteria," draft of unpublished study, in OTC Vol. 040272.

(3) Connell, J., "Analysis of Nasal Airflow Study Designed for the Determination of 'Rebound Congestion' from the 'Benzedrex' Inhaler," draft of unpublished study, in OTC Vol. 040272.

(4) Harvey, S. C., "Sympathomimetic Drugs," in "Remington's Pharmaceutical Sciences," 18th ed., edited by A. R. Gennaro et al., Mack Printing Co., Easton, PA, p. 884, 1990.

(5) Hoffman, B. B., and R. J. Lefkowitz, "Catecholamines and the Sympathomimetic Drugs," in "The Pharmacological Basis of

Therapeutics," 8th ed., edited by A. G. Gilman et al., Pergamon Press, Inc., New York, p. 216, 1990.

II. Summary of Significant Changes From the Proposed Rule

1. In order to allow for flexibility in the labeling of products, the agency has revised the indications in § 341.80(b)(1) to allow manufacturers to choose from among any of the indications (i.e., the common cold (cold), allergic rhinitis, or sinusitis) for nasal decongestant drug products that are consistent with the intended use of the product. (See comment 14 in section I.E. of this document)

2. The agency is not including proposed § 341.80(b)(2), "Other allowable indications" in this final monograph, but is revising and incorporating the statements proposed in that section of the tentative final monograph into the indications included in § 341.80(b)(2) of this final monograph. (See comments 13 and 16 in section I.E. of this document.)

3. Because the phrases "For the temporary relief of" and "Temporarily relieves" are interchangeable, the option of using either phrase is included in § 341.80(b) of the final monograph. (See comment 15 in section I.E. of this document.)

4. The agency is including the term "sinus congestion" in the indications in § 341.80(b)(2)(iv) and (v), and the word "temporarily" has also been added so that the phrase reads: "* * * temporarily relieves sinus congestion and pressure." (See comments 16 and 17 in section I.E. of this document.)

5. In order to conform to numbering specified in 1 CFR 21.11(h), the numbering of many of the warnings proposed in § 341.80(c) has been changed. Specifically, paragraphs (*a*) through (*d*) have been designated as (A) through (D) in this final monograph. Likewise, in the directions proposed in § 341.80(d), paragraphs (*a*) and (*b*) have been designated as (A) and (B).

6. The agency has revised the warning for oral nasal decongestants in proposed § 341.80(c)(1)(i)(*a*) and (c)(1)(ii)(*a*) (designated as § 341.80(c)(1)(i)(A) and (c)(1)(ii)(A) in this final monograph) to provide the information in two separate statements. The agency is also requiring that the first part of the warning appears on the label of the product in boldface type so that the warnings now read as follows: "Do not exceed recommended dosage. [first sentence in boldface type] If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a doctor." (See comment 26 in section I.E. of this document.)

7. The agency has revised the warning for oral nasal decongestants in proposed § 341.80(c)(1)(i)(*b*) and (c)(1)(ii)(*b*) (designated as § 341.80(c)(1)(i)(B) and (c)(1)(ii)(B) in this final monograph) to delete the language that restricted use of the product to only 7 days. The revised warning reads as follows: "If symptoms do not improve within 7 days or are accompanied by fever, consult a doctor." (See comment 21 in section I.E. of this document.)

8. To be consistent with the wording of other warnings for children, the agency has revised the warning proposed in § 341.80(c)(1)(ii)(*c*) (designated as § 341.80(c)(1)(ii)(C) in this final monograph), "Do not give this product to children who have heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor," as follows: "Do not give this product to a child who has heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor." Likewise, the warning proposed in § 341.80(c)(2)(ix)(*b*) (designated as § 341.80(c)(2)(viii)(B) in this final monograph), "Do not use this product in children who have heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor," has been revised as follows: "Do not use this product in a child who has heart disease * * *."

9. The agency has divided the warning for topical nasal decongestants proposed in § 341.80(c)(2)(i)(A) into two separate warnings and is requiring that the first warning appear on the label of the product in boldface type as follows: "Do not exceed recommended dosage." [sentence in boldface type] and "This product may cause temporary discomfort such as burning, stinging, sneezing, or an increase in nasal discharge." These two warnings are being included in the final monograph in § 341.80(c)(2)(i)(A) and (c)(2)(i)(B), respectively. Inclusion of these two warnings has necessitated a change of proposed § 341.80(c)(2)(i)(*b*) to § 341.80(c)(2)(i)(C). (See comment 27 in section I.E. of this document.)

10. To inform and warn consumers about the possibility of the occurrence of rebound congestion with prolonged and excessive use of topical nasal decongestants, the agency has expanded the warning in proposed § 341.80(c)(2)(iii)(*a*), § 341.80(c)(2)(vi), § 341.80(c)(2)(ix), and § 341.80(c)(2)(x) (designated as § 341.80(c)(2)(iii)(A), § 341.80(c)(2)(v), § 341.80(c)(2)(viii), and § 341.80(c)(2)(ix), respectively, in this final monograph) as follows: "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor." (See comment 2 in section I.A. of this document.)

11. The agency is deleting the warning proposed for 1 percent phenylephrine hydrochloride in § 341.80(c)(2)(v) and is instead requiring that 1 percent phenylephrine bear the warning for all topical nasal decongestants in § 341.80(c)(2)(iii)(A). (See comment 2 in section I.A. of this document and comment 28 in section I.E. of this document.)

12. To be consistent with the drug interaction precaution statement used for OTC antitussive and bronchodilator drug products, the agency has revised § 341.80(c)(1)(i)(*d*) (now designated as § 341.80(c)(1)(i)(D)) to read:

Drug interaction precaution. Do not use this product if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your prescription drug contains an MAOI, consult a health professional before taking this product.

The drug interaction precaution statement in § 341.80(c)(1)(ii)(*d*) (now designated as § 341.80(c)(1)(ii)(D)) is similarly revised to read:

Drug interaction precaution. Do not give this product to a child who is taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your child's prescription drug contains an MAOI, consult a health professional before giving this product.

(See comment 22 in section I.E. of this document.)

13. The agency is adding § 341.80(d)(2)(iv)(A)(*2*) for 0.025-percent aqueous oxymetazoline hydrochloride solution to provide for use by children 2 to under 6 years of age, and removing § 341.90(m). (See comment 8 in section I.C. of this document.)

14. The agency is revising § 341.80(d)(2)(vii)(A)(*2*) for 0.05-percent aqueous xylometazoline hydrochloride solution to provide for use by children 2 to under 6 years of age. The agency also is not including proposed § 341.90(n) in this final monograph. (See comment 8 in section I.C. of this document.)

15. The agency is adding the statement "Use only recommended amount." to the directions for oxymetazoline hydrochloride (§ 341.80(d)(2)(iv)(A)(*2*)), xylometazoline hydrochloride (§ 341.80(d)(2)(vii)(A)(*2*)), and

phenylephrine hydrochloride (§ 341.80(d)(2)(v)(A)(4)) products labeled for use by children 2 to under 6 years of age. The agency is also requiring that such products have either a calibrated dropper or a metered-dose spray that delivers no more than a stated amount of drug per three drops or three sprays. (See comment 8 in section I.C. of this document.)

16. The agency has revised the directions statements, where appropriate, as follows: "Adults and children 12 years of age and over,". The agency has added the phrase "* * * and children 12 years of age and over" to the directions to clarify that the 12 years and over age group should receive an adult dose.

17. The agency is not including proposed § 341.80(e) (which states: "The word 'physician' may be substituted for the word 'doctor' in any of the labeling statements above.") in this final monograph because the agency has amended § 330.1 (21 CFR 330.1) to permit the interchangeability of certain terms, including "physician" and "doctor," in all OTC drug monographs. (See 59 FR 3998, January 28, 1994.)

18. The agency is revising the paragraph designations in § 341.3 *Definitions* in that § 341.3(e) and (f) are being changed to § 345.3(f) and (g), respectively) and is adding new § 341.3(h) for *Calibrated dropper*. (See comment 8 in section I.C. of this document.)

19. The agency has determined that for an active ingredient to be included in an OTC drug final monograph, it is necessary to have publicly available chemical information that can be used by all manufacturers to determine that the ingredient is appropriate for use in their products. Because l-desoxyephedrine and racephedrine hydrochloride are not currently standardized and characterized for quality and purity in official compendia, i.e., the United States Pharmacopeia (U.S.P.), they are not included in this final monograph. However, should interested parties develop appropriate standards that are included in the U.S.P., this final monograph will be amended to include one or both of these ingredients. In the interim, the final monograph will be reserved for entries for l-desoxyephedrine and racephedrine hydrochloride as topical nasal decongestants. These ingredients are being included in § 310.545(a)(6)(ii)(B), nonmonograph ingredients, until appropriate compendial standards are developed.

III. The Agency's Final Conclusions on OTC Nasal Decongestant Drug Products

Based on the available evidence, the agency is issuing a final monograph establishing conditions under which OTC nasal decongestant drug products are generally recognized as safe and effective and not misbranded. Specifically, the following ingredients are included in this final monograph as OTC oral nasal decongestants: Phenylephrine hydrochloride, pseudoephedrine hydrochloride, and pseudoephedrine sulfate. The following ingredients are included as topical nasal decongestants: Ephedrine, ephedrine hydrochloride, ephedrine sulfate, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, propylhexedrine, and xylometazoline hydrochloride. The status of phenylpropanolamine preparations as an oral nasal decongestant is deferred at this time. All other ingredients for OTC nasal decongestant use in this rulemaking are considered nonmonograph ingredients: Beechwood creosote (topical), bornyl acetate (topical), camphor (topical), cedar leaf oil (topical), l-desoxyephedrine (topical), ephedrine (oral), ephedrine hydrochloride (oral), ephedrine sulfate (oral), racephedrine hydrochloride (oral/topical), eucalyptol/eucalyptus oil (topical), menthol/peppermint oil (topical), allyl isothiocyanate (mustard oil) (topical), thenyldiamine hydrochloride (topical), thymol (topical), and turpentine oil (spirits of turpentine) (topical). The agency has established 21 CFR 310.545 in which it lists certain active ingredients that are not generally recognized as safe and effective for certain OTC drug uses. The following ingredients are presently listed in 21 CFR 310.545(a)(6)(ii) for nasal decongestant drug products: Allyl isothiocyanate, camphor (lozenge), beechwood creosote (oral), eucalyptol (lozenge), eucalyptol (mouthwash), eucalyptus oil (lozenge), eucalyptus oil (mouthwash), menthol (mouthwash), peppermint oil (mouthwash), thenyldiamine hydrochloride, thymol, thymol (lozenge), thymol (mouthwash), and turpentine oil. In this final rule, the agency is amending 21 CFR 310.545(a)(6)(ii) by adding the following nasal decongestant ingredients: Beechwood creosote (topical), bornyl acetate (topical), cedar leaf oil (topical), l-desoxyephedrine (topical), ephedrine (oral), ephedrine hydrochloride (oral), ephedrine sulfate (oral), and racephedrine hydrochloride (oral/topical). These ingredients appear in new § 310.545(a)(6)(ii)(B), while previous § 310.545(a)(6)(ii) is redesignated § 310.545(a)(6)(ii)(A). Any drug product marketed for use as an OTC nasal decongestant that is not in conformance with the monograph (21 CFR part 341, subparts A, B, and C) is considered a new drug within the meaning of section 201(p) of the act (21 U.S.C. 321(p)) and misbranded under section 502 of the act and cannot be marketed for this use unless it is the subject of an approved application. An appropriate citizen petition to amend the monograph may also be submitted under 21 CFR 10.30.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (50 FR 2220 at 2238). FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96–354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. This final rule will require some relabeling for products containing monograph ingredients. Manufacturers will have 1 year to implement this relabeling. This final rule will also require reformulation of any products containing beechwood creosote (topical), bornyl acetate (topical), cedar leaf oil (topical), l-desoxyephedrine (topical), ephedrine sulfate (oral), and racephedrine hydrochloride (oral/topical). For all other nonmonograph ingredients listed above, the effective date was May 7, 1991. The impact to the final rule appears to be minimal. Accordingly, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the regulatory flexibility Act, no further analysis is required.

The agency is removing existing warning and caution statements in § 369.20 for "NASAL PREPARATIONS: OIL BASE," "NASAL PREPARATIONS

IN PLASTIC SPRAY CONTAINERS," "NASAL PREPARATIONS: 'ASOCONSTRICTORS (AMPHETAMINE, EPHEDRINE, EPINEPHRINE, METHAMPHETAMINE, AND OTHERS OF SIMILAR ACTIVITY)," "PHENYLEPHRINE HYDROCHLORIDE PREPARATIONS, ORAL" and the terms "PHENYLEPHRINE HYDROCHLORIDE, HYDROXYAMPHETAMINE" and "AND OTHERS OF SIMILAR ACTIVITY" in the entry "NASAL PREPARATIONS: VASOCONSTRICTORS (PHENYLEPHRINE HYDROCHLORIDE, HYDROXYAMPHETAMINE, PHENYLPROPANOLAMINE, AND OTHERS OF SIMILAR ACTIVITY)" because these portions of the regulations are superseded by the requirements of the nasal decongestant final monograph (21 CFR part 341).

List of Subjects

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 341

Labeling, Over-the-counter drugs.

21 CFR Part 369

Labeling, Medical devices, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 310, 341, and 369 are amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512–516, 520, 601(a), 701, 704, 705, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 379e); secs. 215, 301, 302(a), 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b–263n).

2. Section 310.545 is amended by redesignating the text of paragraph (a)(6)(ii) as paragraph (a)(6)(ii)(A), by adding new (a)(6)(ii)(A) heading and paragraphs (a)(6)(ii)(B) and (d)(23), and by revising paragraph (d) introductory text and paragraph (d)(1) to read as follows:

§ 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.

(a) * * *

(6) * * *

(ii) *Nasal decongestant drug products*—(A) *Approved as of May 7, 1991.* * * *

(B) *Approved as of August 23, 1995.*

Bornyl acetate (topical)
Cedar leaf oil (topical)
Creosote, beechwood (topical)
l-desoxyephedrine (topical)
Ephedrine (oral)
Ephedrine hydrochloride (oral)
Ephedrine sulfate (oral)
Racephedrine hydrochloride (oral/topical)

* * * * *

(d) Any OTC drug product that is not in compliance with this section is subject to regulatory action if initially introduced or initially delivered for introduction into interstate commerce after the dates specified in paragraphs (d)(1) through (d)(23) of this section.

(1) May 7, 1991, for products subject to paragraphs (a)(1) through (a)(2)(i), (a)(3) through (a)(6)(i)(A), (a)(6)(ii)(A), (a)(7) (except as covered by paragraph (d)(3) of this section), (a)(8)(i), (a)(9) through (a)(10)(iii), and (a)(11) through (a)(18)(i) of this section.

* * * * *

(23) August 23, 1995, for products subject to paragraph (a)(6)(ii)(B) of this section.

PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTIASTHMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

3. The authority citation for 21 CFR part 341 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

4. Section 341.3 is amended by adding new paragraphs (f), (g), and (h) to read as follows:

§ 341.3 Definitions.

* * * * *

(f) *Oral nasal decongestant drug.* A drug that is taken by mouth and acts systemically to reduce nasal congestion caused by acute or chronic rhinitis.

(g) *Topical nasal decongestant drug.* A drug that when applied topically inside the nose, in the form of drops, jellies, or sprays, or when inhaled intranasally reduces nasal congestion caused by acute or chronic rhinitis.

(h) *Calibrated dropper.* A dropper calibrated such that the volume error incurred in measuring any liquid does not exceed 15 percent under normal use conditions.

5. Section 341.20 is added to subpart B to read as follows:

§ 341.20 Nasal decongestant active ingredients.

The active ingredient of the product consists of any of the following when used within the dosage limits and in the dosage forms established for each ingredient:

(a) *Oral nasal decongestants.* (1) Phenylephrine hydrochloride.
(2) Pseudoephedrine hydrochloride.
(3) Pseudoephedrine sulfate.

(b) *Topical nasal decongestants.* (1) [Reserved]
(2) Ephedrine.
(3) Ephedrine hydrochloride.
(4) Ephedrine sulfate.
(5) [Reserved]
(6) Naphazoline hydrochloride.
(7) Oxymetazoline hydrochloride.
(8) Phenylephrine hydrochloride.
(9) Propylhexedrine.
(10) Xylometazoline hydrochloride.

6. Section 341.80 is added to subpart C to read as follows:

§ 341.80 Labeling of nasal decongestant drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "nasal decongestant."

(b) *Indications.* The labeling of the product states, under the heading "Indications," the phrase listed in paragraph (b)(1) of this section, as appropriate, and may contain any additional phrases listed in paragraph (b)(2) of this section. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in paragraphs (b)(1) and (b)(2) of this section, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) (Select one of the following: "For the temporary relief of nasal congestion" or "Temporarily relieves nasal congestion") (which may be followed by any of the following in paragraphs (b)(1) (i), (ii), and (iii) of this section):

(i) "due to" (select one of the following: "the common cold" or "a cold").

(ii) "due to" (select one of the following: "hay fever," "hay fever (allergic rhinitis)," "hay fever or other upper respiratory allergies," or "hay fever or other upper respiratory allergies (allergic rhinitis)").

(iii) "associated with sinusitis."

(2) In addition to the information identified in paragraph (b)(1) of this section, the labeling of the product may contain any (one or more) of the following statements:

(i) (Select one of the following: "For the temporary relief of" or "Temporarily relieves") (select one of the following: "stuffy nose," "stopped up nose," "nasal stuffiness," or "clogged up nose.")

(ii) (Select one of the following: "Reduces swelling of," "Decongests," or "Helps clear") "nasal passages; shrinks swollen membranes."

(iii) "Temporarily restores freer breathing through the nose."

(iv) "Helps decongest sinus openings and passages; temporarily relieves sinus congestion and pressure."

(v) "Promotes nasal and/or sinus drainage; temporarily relieves sinus congestion and pressure."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *Oral nasal decongestants*—(i) *For products containing phenylephrine hydrochloride, pseudoephedrine hydrochloride, or pseudoephedrine sulfate identified in § 341.20 (a)(1), (a)(2), and (a)(3) when labeled for adults.* (A) "Do not exceed recommended dosage. [first sentence in boldface type] If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a doctor."

(B) "If symptoms do not improve within 7 days or are accompanied by fever, consult a doctor."

(C) "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

(D) "*Drug interaction precaution.* Do not use this product if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your prescription drug contains an MAOI, consult a health professional before taking this product."

(ii) *For products containing phenylephrine hydrochloride, pseudoephedrine hydrochloride, or pseudoephedrine sulfate identified in § 341.20 (a)(1), (a)(2), and (a)(3) when labeled for children under 12 years of age.* (A) "Do not exceed recommended dosage. [first sentence in boldface type] If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a doctor."

(B) "If symptoms do not improve within 7 days or are accompanied by fever, consult a doctor."

(C) "Do not give this product to a child who has heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor."

(D) "*Drug interaction precaution.* Do not give this product to a child who is taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your child's prescription drug contains an MAOI, consult a health professional before giving this product."

(iii) *For oral nasal decongestant products labeled for both adults and children under 12 years of age.* The labeling of the product contains the warnings identified in paragraph (c)(1)(i) of this section.

(2) *Topical nasal decongestants*—(i) *For products containing any topical nasal decongestant identified in § 341.20(b) when labeled for adults.* (A) "Do not exceed recommended dosage." [sentence in boldface type]

(B) "This product may cause temporary discomfort such as burning, stinging, sneezing, or an increase in nasal discharge."

(C) "The use of this container by more than one person may spread infection."

(ii) [Reserved]

(iii) *For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, or xylometazoline hydrochloride identified in § 341.20 (b)(2), (b)(3), (b)(4), (b)(6), (b)(7), (b)(8), and (b)(10) when used as nasal sprays, drops, or jellies and when labeled for adults.* (A) "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor."

(B) "Do not use this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

(iv) *For products containing naphazoline hydrochloride identified in § 341.20(b)(6) at a concentration of 0.05 percent.* "Do not use this product in children under 12 years of age because it may cause sedation if swallowed."

(v) *For products containing propylhexedrine identified in § 341.20(b)(9) when used in an inhalant dosage form and when labeled for adults.* "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor."

(vi) *For products containing any topical nasal decongestant identified in § 341.20(b) when labeled for children under 12 years of age.* The labeling of the product contains the warnings identified in paragraph (c)(2)(i) of this section.

(vii) [Reserved]

(viii) *For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, or xylometazoline hydrochloride identified in § 341.20(b)(2), (b)(3), (b)(4), (b)(6), (b)(7), (b)(8), and (b)(10) when used as nasal sprays, drops, or jellies and when labeled for children under 12 years of age.* (A) "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor."

(B) "Do not use this product in a child who has heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor."

(ix) *For products containing propylhexedrine identified in § 341.20(b)(9) when used in an inhalant dosage form and when labeled for children under 12 years of age.* "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor."

(x) *For topical nasal decongestant products labeled for both adults and for children under 12 years of age.* The labeling of the product contains the applicable warnings identified in paragraphs (c)(2)(i), (c)(2)(ii), (c)(2)(iii), and (c)(2)(v) of this section.

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions":

(1) *Oral nasal decongestants*—(i) *For products containing phenylephrine hydrochloride identified in § 341.20(a)(1).* Adults and children 12 years of age and over: 10 milligrams every 4 hours not to exceed 60 milligrams in 24 hours. Children 6 to under 12 years of age: 5 milligrams every 4 hours not to exceed 30 milligrams in 24 hours. Children 2 to under 6 years of age: 2.5 milligrams every 4 hours not to exceed 15 milligrams in 24 hours. Children under 2 years of age: consult a doctor.

(ii) *For products containing pseudoephedrine hydrochloride or*

pseudoephedrine sulfate identified in § 341.20 (a)(2) and (a)(3). Adults and children 12 years of age and over: 60 milligrams every 4 to 6 hours not to exceed 240 milligrams in 24 hours. Children 6 to under 12 years of age: 30 milligrams every 4 to 6 hours not to exceed 120 milligrams in 24 hours. Children 2 to under 6 years of age: 15 milligrams every 4 to 6 hours not to exceed 60 milligrams in 24 hours. Children under 2 years of age: consult a doctor.

(2) *Topical nasal decongestants*—(i) [Reserved]

(ii) *For products containing ephedrine, ephedrine hydrochloride, or ephedrine sulfate identified in § 341.20(b) (2), (3), and (4)*—(A) *Nasal drops or sprays—For a 0.5-percent aqueous solution.* Adults and children 12 years of age and over: 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Children 6 to under 12 years of age (with adult supervision): 1 or 2 drops or sprays in each nostril not more often than every 4 hours. Children under 6 years of age: consult a doctor.

(B) *Nasal jelly—For a 0.5-percent water-based jelly.* Adults and children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 4 hours.

(iii) *For products containing naphazoline hydrochloride identified in § 341.20(b)(6)*—(A) *Nasal drops or sprays—(1) For a 0.05-percent aqueous solution.* Adults and children 12 years of age and over: 1 or 2 drops or sprays in each nostril not more often than every 6 hours. Do not give to children under 12 years of age unless directed by a doctor.

(2) *For a 0.025-percent aqueous solution.* Children 6 to under 12 years of age (with adult supervision): 1 or 2 drops or sprays in each nostril not more often than every 6 hours. Children under 6 years of age: consult a doctor.

(B) *Nasal jelly—(1) For a 0.05-percent water-based jelly.* Adults and children 12 years of age and over: place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 6 hours. Do not give to children under 12 years of age unless directed by a doctor.

(2) *For a 0.025-percent water-based jelly.* Children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 6 hours. Children under 6 years of age: consult a doctor.

(iv) *For products containing oxymetazoline hydrochloride identified in § 341.20(b)(7)*—(A) *Nasal drops or sprays—(1) For a 0.05-percent aqueous solution.* Adults and children 6 to under 12 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 10 to 12 hours. Do not exceed 2 doses in any 24-hour period. Children under 6 years of age: consult a doctor.

(2) *A 0.025-percent aqueous solution in a container having either a calibrated dropper or a metered-dose spray that delivers no more than 0.027 milligrams of oxymetazoline per three drops or three sprays.* Children 2 to under 6 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 10 to 12 hours. Use only recommended amount. Do not exceed 2 doses in any 24-hour period. [previous two sentences in boldface type] Children under 2 years of age: consult a doctor.

(B) *Nasal jelly—For a 0.05-percent water-based jelly.* Adults and children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 10 to 12 hours. Do not exceed 2 doses in any 24-hour period. Children under 6 years of age: consult a doctor.

(v) *For products containing phenylephrine hydrochloride identified in § 341.20(b)(8)*—(A) *Nasal drops or sprays—(1) For a 1-percent aqueous solution.* Adults and children 12 years of age and over: 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Do not give to children under 12 years of age unless directed by a doctor.

(2) *For a 0.5-percent aqueous solution.* Adults and children 12 years of age and over: 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Do not give to children under 12 years of age unless directed by a doctor.

(3) *For a 0.25-percent aqueous solution.* Adults and children 6 to under 12 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Children under 6 years of age: consult a doctor.

(4) *A 0.125-percent aqueous solution in a container having either a calibrated dropper or a metered-dose spray that delivers no more than 0.135 milligrams of phenylephrine per three drops or three sprays.* Children 2 to under 6 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Use only recommended amount. [previous sentence in boldface type] Children under 2 years of age: consult a doctor.

(B) *Nasal jelly—(1) For a 1-percent water-based jelly.* Adults and children 12 years of age and over: place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 4 hours. Do not give to children under 12 years of age unless directed by a doctor.

(2) *For a 0.5-percent water-based jelly.* Adults and children 12 years of age and over: place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 4 hours. Do not give to children under 12 years of age unless directed by a doctor.

(3) *For a 0.25-percent water-based jelly.* Adults and children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 4 hours. Children under 6 years of age: consult a doctor.

(vi) *For products containing propylhexedrine identified in § 341.20(b)(9) when used in an inhalant dosage form.* The product delivers in each 800 milliliters of air 0.40 to 0.50 milligrams of propylhexedrine. Adults and children 6 to under 12 years of age (with adult supervision): 2 inhalations in each nostril not more often than every 2 hours. Children under 6 years of age: consult a doctor.

(vii) *For products containing xylometazoline hydrochloride identified in § 341.20(b)(10)*—(A) *Nasal drops or sprays—(1) For a 0.1-percent aqueous solution.* Adults and children 12 years of age and over: 2 or 3 drops or sprays in each nostril not more often than every 8 to 10 hours. Do not give to children under 12 years of age unless directed by a doctor.

(2) *A 0.05-percent aqueous solution in a container having either a calibrated dropper or a metered-dose spray that delivers no more than 0.054 milligrams of xylometazoline per three drops or three sprays.* Children 6 to under 12 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 8 to 10 hours. Children 2 to under 6 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 8 to 10 hours. Use only recommended amount. Do not exceed 3 doses in any 24-hour period. [previous two sentences in boldface type] Children under 2 years of age: consult a doctor.

(B) *Nasal jelly—(1) For a 0.1-percent water-based jelly.* Adults and children 12 years of age and over: place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 8 to 10 hours. Do not give to children under 12 years of age unless directed by a doctor.

(2) *For a 0.05-percent water-based jelly.* Children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 8 to 10 hours. Children under 6 years of age: consult a doctor.

(viii) *Other required statements—For products containing propylhexedrine identified in § 341.20(b)(9) when used in an inhalant dosage form.* (A) "This inhaler is effective for a minimum of 3 months after first use."

(B) "Keep inhaler tightly closed."

PART 369—INTERPRETATIVE STATEMENTS RE WARNINGS ON DRUGS AND DEVICES FOR OVER-THE-COUNTER SALE

7. The authority citation for 21 CFR part 369 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371).

§ 369.20 [Amended]

8. Section 369.20 *Drugs; recommended warning and caution statements* is amended by removing the entries for "NASAL PREPARATIONS: OIL BASE," "NASAL PREPARATIONS IN PLASTIC SPRAY CONTAINERS," "NASAL PREPARATIONS: VASOCONSTRICTORS (AMPHETAMINE, EPHEDRINE, EPINEPHRINE, METHAMPHETAMINE AND OTHERS OF SIMILAR ACTIVITY)," "PHENYLEPHRINE HYDROCHLORIDE PREPARATIONS, ORAL," and the terms "PHENYLEPHRINE HYDROCHLORIDE, HYDROXYAMPHETAMINE" and "AND OTHERS OF SIMILAR ACTIVITY" in the entry "NASAL PREPARATIONS: VASOCONSTRICTORS (PHENYLEPHRINE HYDROCHLORIDE, HYDROXYAMPHETAMINE, PHENYLPROPANOLAMINE, AND OTHERS OF SIMILAR ACTIVITY)."

Dated: August 4, 1994.

Michael R. Taylor,

Deputy Commissioner for Policy.

[FR Doc. 94–20456 Filed 8–22–94; 8:45 am]

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Proposed Rules

Federal Register
Vol. 69, No. 211
Tuesday, November 2, 2004

This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 341

[Docket No. 1976N–0052N]

RIN 0910–AF34

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Proposed Amendment of Monograph for Over-the-Counter Nasal Decongestant Drug Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the final monograph (FM) for over-the-counter (OTC) nasal decongestant drug products (drug products used to relieve nasal congestion due to a cold, hay fever, or other upper respiratory allergies) to add phenylephrine bitartrate as generally recognized as safe and effective (GRASE) when used in an effervescent tablet. An effervescent tablet is intended to be dissolved in water before taking by mouth. This proposal is part of FDA's ongoing review of OTC drug products.

DATES: Submit written or electronic comments and comments on FDA's economic impact determination by January 31, 2005. Please see section X of this document for the effective date of any final rule that may publish based on this proposal.

ADDRESSES: You may submit comments, identified by Docket No. 1976N–0052N and/or RIN number 0910–AF34, by any of the following methods:

- Federal eRulemaking Portal: *http://www.regulations.gov*. Follow the instructions for submitting comments.
- Agency Web site: *http://www.fda.gov/dockets/ecomments*. Follow the instructions for submitting comments on the agency Web site.
- E-mail: *fdadockets@oc.fda.gov*. Include Docket No. 1976N–0052N and/or RIN number 0910–AF34 in the subject line of your e-mail message.
- FAX: 301-827-6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD–ROM submissions]: Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the agency name and Docket No. 1976N–0052N or Regulatory Information Number 0910–AF34 (RIN) for this rulemaking. All comments received will be posted without change to *http://www.fda.gov/ohrms/dockets/default.htm*, including any personal information provided. For detailed instructions on submitting comments and additional information on the rulemaking process, see the ''Comments'' heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.fda.gov/ohrms/dockets/default.htm* and insert the docket number(s), found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Houda Mahayni, Center for Drug Evaluation and Research (HFD–560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2222.

SUPPLEMENTARY INFORMATION:

I. Background

A. Advance Notice of Proposed Rulemaking (ANPRM)

1. OTC Cough-Cold Drug Products

In the **Federal Register** of September 9, 1976 (41 FR 38312), FDA published the report of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (Cough-Cold Panel). That Panel reviewed oral and topical nasal decongestant drug products and found phenylephrine hydrochloride to be a safe and effective ingredient for OTC use (41 FR 38312 at 38399 and 38400). The Cough-Cold Panel did not evaluate phenylephrine bitartrate.

2. OTC Oral Health Care Drug Products

In the **Federal Register** of May 25, 1982 (47 FR 22760), FDA published the report of the Advisory Review Panel on OTC Oral Cavity Drug Products (Oral Cavity Panel). That Panel reviewed the safety and effectiveness of two oral nasal decongestant ingredients, phenylephrine hydrochloride and phenylpropanolamine hydrochloride (in lozenge form), and classified these ingredients as Category III (more data needed) (47 FR 22760 at 22911 through 22914). The Oral Cavity Panel did not evaluate phenylephrine bitartrate.

B. Tentative Final Monograph (TFM)

1. OTC Cough-Cold Drug Products

In the **Federal Register** of January 15, 1985 (50 FR 2220), FDA published the TFM for OTC nasal decongestant drug products. The TFM proposed phenylephrine hydrochloride as a monograph ingredient but did not address phenylephrine bitartrate.

2. OTC Oral Health Care Drug Products

In the **Federal Register** of January 27, 1988 (53 FR 2436), FDA published the TFM for OTC oral health care (anesthetic/analgesic, astringent, debriding agent/oral wound cleanser, and demulcent) drug products. FDA referred the data on the oral nasal decongestant ingredients phenylephrine hydrochloride and phenylpropanolamine hydrochloride to the rulemaking for OTC nasal decongestant drug products because that was the primary rulemaking for these ingredients (53 FR 2436 at 2448 and 2449).

C. Final Monograph (FM)

1. OTC Cough-Cold Drug Products

In the **Federal Register** of August 23, 1994 (59 FR 43386), FDA published the FM for OTC nasal decongestant drug products. The monograph included phenylephrine hydrochloride as GRASE for oral and topical use as a nasal decongestant (§ 341.20(a) and (b)(8) (21 CFR 341.20(a) and (b)(8))). FDA acknowledged that phenylephedrine bitartrate was submitted as an oral nasal decongestant active ingredient in an effervescent combination cold tablets for OTC use. FDA noted that the ingredient was not reviewed by the Cough-Cold Panel or included in its report, or addressed in the TFM for OTC nasal

decongestant drug products (59 FR 43386 at 43394 and 43395). FDA reviewed data on phenylephedrine bitartrate submitted in a comment and concluded that the data were inadequate to demonstrate the safety and effectiveness of phenylephrine bitartrate as an OTC oral nasal decongestant ingredient. Consequently, this ingredient was not included in the FM.

2. OTC Oral Health Care Drug Products

FDA has not published an FM for these products.

II. Citizen Petition

A manufacturer submitted a citizen petition (Ref. 1) requesting FDA to amend the OTC nasal decongestant FM to include the ingredient phenylephrine bitartrate as GRASE in an effervescent tablet. The manufacturer stated:

- Domestic and international marketing experiences meet FDA's material time and extent criteria for inclusion in an OTC drug monograph.
- In vitro and in vivo studies demonstrate comparability of phenylephrine bitartrate with phenylephrine hydrochloride, an approved monograph active ingredient.
- Phenylephrine bitartrate would provide consumers a greater choice in combination nasal decongestant/analgesic cough-cold formulations.

The manufacturer requested GRASE status for phenylephrine bitartrate for use as a single ingredient or in combination with any monograph cough-cold active ingredient(s) when delivered in an effervescent tablet.

III. FDA's Comments on the Citizen Petition

A. Marketing History

According to the manufacturer, consumers have used phenylephrine hydrochloride and bitartrate domestically and globally as a nasal decongestant for decades. In terms of domestic marketing experience, the following drug products containing phenylephrine bitartrate have been marketed in the United States: (1) An effervescent product containing aspirin, chlorpheniramine maleate, and phenylephrine bitartrate marketed OTC from 1968 to 1976, before being voluntarily discontinued by its manufacturer, and (2) an inhalation product containing isoproterenol hydrochloride and phenylephrine bitartrate marketed by prescription and later discontinued. Phenylephrine bitartrate containing products have been marketed outside the United States (Central America, Mexico, Australia, and Spain) since 1978. As of 2002, a total of 1.16 billion tablets have been distributed in these countries (Ref. 1).

Products containing bitartrate are presently sold by prescription in the United States as a salt of hydrocodone, dihydrocodone, and dihydrocodeine. Phenylephrine bitartrate is similar to phenylephrine hydrochloride, which is currently included as an oral nasal decongestant active ingredient in § 341.20(a)(1). Both phenylephrine salts have the same pharmacologic activity and similar side effects. FDA is aware that phenylephrine bitratrate effervescent tablets were marketed in the United States in the 1960s and 1970s and had a similar use and adverse reaction profile as products containing phenylephrine hydrochloride. The citizen petition provides sufficient information of marketing outside the United States since 1978 to allow FDA to determine that phenylephrine bitartrate as a nasal decongestant has been marketed to a material time and to a material extent. In addition, the citizen petition contains recent data demonstration that the phenylephrine bitartrate salt is bioavailable and comparable to the phenylephrine hydrochloride salt.

B. Safety and Effectiveness

1. Review of Adverse Event Databases (AEDs)

The manufacturer conducted a safety review of the FDA and World Health Organization's (WHO) AEDs concerning phenylephrine bitartrate for the period from 1969 to 1997. The review included all dosage forms of phenylephrine but was nonspecific for the phenylephrine salt (e.g., hydrochloride or bitartrate). The review identified 22 reports for phenylephrine bitartrate out of approximately 900 reports for phenylephrine administered orally. There were five reports of ''no drug effect'', two reports of nervousness, and 15 different single events reported such as rash, vomiting, diarrhea, and insomnia. The manufacturer commented that causality and preexisting conditions in the 22 reported subjects could not be established from the available data. The manufacturer noted that:

- The FDA database does not indicate the relationship of adverse events or preexisting medical conditions of consumers to the administration of phenylephrine.
- The WHO database revealed five different single event reports for products containing phenylephrine bitartrate as an active ingredient.
- Reports provided by the manufacturer's affiliate from other countries in which phenylephrine bitartrate products are marketed provided no information on adverse events relative to phenylephrine bitartrate.

FDA finds these data suggest that there are no significant safety concerns reported from the use of phenylephrine bitartrate in the countries where it is currently used. Safety information from various U.S. databases is not available specifically for phenylephrine bitartrate because it has not been marketed for the past 30 years. Safety information from U.S. databases indicate that phenylephrine hydrochloride is safe for OTC use within the label warnings in § 341.80(c)(1) (21 CFR 341.80(c)(1)). Based on their similar pharmacologic activity and side effects, FDA has determined that both phenylephrine salts are safe for OTC use.

2. Pharmacokinetic Study

In a meeting held on February 15, 2002 (Ref. 2), FDA suggested that the manufacturer conduct a bioequivalence study. FDA recommended that the manufacturer follow FDA's Guidance for Industry entitled ''Bioavailability and Bioequivalence Studies for Orally Administered Drug Products General Considerations'' (the Guidance) (Ref. 3). The Guidance describes a single-dose pharmacokinetic study of both immediate and modified release drug products to demonstrate bioequivalence. FDA generally considers a single-dose study to be more sensitive than a multiple-dose study in assessing the release of the drug substance from the drug product into the systemic circulation. Further, if a multiple-dose study design is necessary, the Guidance recommends performing appropriate dosage administration and sampling to document that ''steady-state'' is attained. At steady-state, the rate of drug leaving the body is equal to the rate of drug entering the body.

The manufacturer submitted an open-label, four-way crossover, multiple-dose study in healthy volunteers to evaluate the pharmacokinetic profiles of the following equivalent phenylephrine doses of phenylephrine hydrochloride and phenylephrine bitartrate in two different dosage forms and different weights because of the different salts forms:

- An effervescent phenylephrine hydrochloride 10 milligram (mg) tablet
- An effervescent phenylephrine bitartrate 15.6 mg tablet

- an encapsulated[1] phenylephrine hydrochloride 10 mg capsule
- an encapsulated phenylephrine bitartrate 15.6 mg capsule

Twenty-five subjects completed the study and were considered evaluable for the pharmacokinetic analysis. All subjects were treated with four oral doses of phenylephrine over a 12-hour period. The first dose was administered at 7 a.m. Subsequent doses were administered 4, 8, and 12 hours later. The analysis provided the mean ratio and 90 percent confidence interval of the derived pharmacokinetic parameters, area under the concentration-time curve (AUC) and maximum plasma concentration (Cmax), after single dose and at steady-state for each treatment.

3. FDA's Evaluation of the Pharmacokinetic Study

Bioequivalence may be determined from a multiple-dose study only after a steady-state plasma drug level has been reached. The time needed to reach the steady-state plasma level is related to the elimination half-life of the drug. It takes approximately 6.6 half-lives to reach 99 percent of steady-state plasma level. If steady-state blood levels are going to be used for the determinations of bioequivalence, both drug products must be administered to steady-state. Based on the comparison of the pharmacokinetic parameters obtained, the bioequivalence or lack of bioequivalence may be determined.

The manufacturer did not conduct a single-dose pharmacokinetic study. The manufacturer performed a study in which four doses of the phenylephrine formulations were administered every 4 hours in 1 day. The elimination half-life of phenylephrine is between 2 and 3 hours. Therefore, it takes between 13.2 (2 x 6.6) and 19.8 (3 x 6.6) hours to reach steady-state, at which time blood levels could be obtained to compare and determine bioequivalence. Thus, the study was not designed to achieve steady-state, nor did the manufacturer document that steady-state was reached, which is necessary to establish bioequivalence. Therefore, the study can only demonstrate comparable bioavailability or similarity, but not bioequivalence. Independent scientific study, did not allow enough time between doses.

Table 1 of this document provides a summary of total phenylephrine pharmacokinetic parameters derived from the first-dose data. First-dose data are being considered because attainment of steady-state was not documented and because it is the most robust observation of the data.

TABLE 1.—SUMMARY OF TOTAL PHENYLEPHRINE PHARMACOKINETIC PARAMETERS-DERIVED FROM FIRST-DOSE DATA-MEAN RATIO, 90 PERCENT CONFIDENCE INTERVAL (CI), AND SIGNIFICANCE (P=0.05) (N=25)

Treatment Comparison	Actual AUCτ Ratio CI p-value	log AUCτ Ratio CI p-value	Actual C_{max} Ratio CI p-value	log C_{max} Ratio CI p-value
PEB–E[1] vs. PEH–E[2]	0.98 0.93–1.03 0.4298	1.00 0.99–1.00 0.5077	1.00 0.93–1.07 0.991	1.00 0.99–1.01 0.8642
PEB–C[3] vs. PEH–C[4]	0.91 0.87–0.96 0.0050	0.98 0.98–0.99 0.0020	0.90 0.85–0.97 0.0137	0.98 0.97–0.99 0.0062

[1]Phenylephrine bitartrate in an effervescent tablet.
[2]Phenylephrine hydrochloride in an effervescent tablet.
[3]Phenylephrine bitartrate in a capsule.
[4]Phenylephrine hydrochloride in a capsule.

Table 1 of this document shows that, for the effervescent tablet, the mean ratio (log transformed) for both the C_{max} and AUC is 1.00 when comparing phenylephrine hydrochloride to phenylephrine bitartrate. The actual ratios range from 0.98 to 1.0. Therefore, the rate and extent of absorption after the first-dose of the phenylephrine bitartrate effervescent tablet are considered similar to those of the phenylephrine hydrochloride effervescent tablet.

Although the manufacturer did not perform a single-dose or a multiple-dose study (to steady-state), the similarity in the rate and extent of absorption of phenylephrine hydrochloride and phenylephrine bitartrate in the effervescent tablets allows FDA to conclude that the bioavailability of the phenylephrine salts in the effervescent tablets is comparable.

Table 1 of this document shows that, for the encapsulated formulation, the actual mean ratio for AUC and C_{max} are 0.91 and 0.90 for AUC and C_{max} respectively. Because this study was not of optimal design, FDA has concerns about the plasma concentration-time curve that is not available because the second dose was administered. FDA cannot conclude that the in vivo performance of the products are similar because of the magnitude of the difference of the actual mean ratios of 0.90 and 0.91 from 1.0. The encapsulated capsule is bioavailable but not bioequivalent to the effervescent tablet.

IV. FDA's Tentative Conclusions

A. Single Ingredient Products

FDA has tentatively determined that phenylephrine bitartrate has been marketed to a material extent and for a material time as a nasal decongestant with no indication of safety concerns. Based on the ingredient's marketing history, absence of safety concerns, and additional data provided in the manufacturer's citizen petition, FDA has determined that the pharmacokinetic study is acceptable in lieu of a clinical trial because of the similarity in the bioavailability of the two effervescent

[1] Encapsulated is a capsule dosage form that was termed ''encapsulated'' by the manufacturer in this study.

tablets. Accordingly, FDA acknowledges that the two salts of phenylephrine could be used in the effervescent tablets interchangeably without any clinically significant impact on the performance of the formulations studied. FDA is proposing that phenylephrine bitartrate in an effervescent tablet be GRASE for use as an OTC oral nasal decongestant. Accordingly, FDA is proposing to amend § 341.20(a)(4) of the FM for OTC nasal decongestant drug products to include phenylephrine bitartrate in an effervescent tablet. However, additional pharmacokinetic data are needed to include the phenylephrine bitartrate capsule formulation in the OTC nasal decongestant FM.

B. Combination Products

The combination of single antihistamine, oral nasal decongestant, and analgesic-antipyretic active ingredients is included in 21 CFR 341.40(c) of the Cough-Cold FM. FDA is proposing to include in the FM the combination of chlorpheniramine maleate (antihistamine), phenylephrine bitartrate (oral nasal decongestant), and aspirin (analgesic-antipyretic) in an effervescent tablet. FDA is including only this specific combination product for the following reasons:

- This is the only combination containing phenylephrine bitartrate that has an OTC marketing history in the United States. It was marketed from 1968 to 1976.
- The bitartrate salt form of the OTC nasal decongestant phenylpropanolamine was reviewed by the Cough-Cold Panel and recommended for monograph status as GRASE (41 FR 38312 at 38400 and 38401).
- The rate and extent of absorption of phenylephrine bitartrate effervescent tablet after the first-dose and at steady-state were similar to those of phenylephrine hydrochloride effervescent tablet. Thus, the two phenylephrine salts appear to have comparable bioavailability. A drug-drug interaction study is not necessary for the combination of chlorpheniramine maleate, phenylephrine bitartrate, and aspirin.

FDA does not have data on any other combination products to include them in the FM at this time. FDA is not aware of other combination products containing phenylephrine bitartrate that may have been marketed. To market any other combination product containing phenylephrine bitartrate, manufacturers will need to submit a new drug application deviation (21 CFR 330.11).

C. Monograph Labeling

FDA is proposing the same uses and warnings for phenylephrine bitartrate as appear in § 341.80(b) and (c)(1) for phenylephrine hydrochloride because these are salt of the same ingredient. Based on historical marketing in the United States, more current marketing in foreign countries, and the pharmacokinetic study, FDA is proposing the following doses:

- Adults and children 12 years of age and over: 15.6 milligrams every 4 hours, not to exceed 62.4 milligrams in 24 hours
- Children 6 to under 12 years of age: 7.8 milligrams every 4 hours, not to exceed 31.2 milligrams in 24 hours
- Children under 6 years of age: ask a doctor

FDA proposes that manufacturers include in their product labeling information on the number of tablets and the quantity of water the tablets are to be dissolved in prior to administration.

FDA is also proposing to define effervescent tablet in 21 CFR 341.3 to state:

Effervescent tablet. A tablet intended to be dissolved in water before administration. It contains, in addition to the active ingredient(s), mixtures of acids (citric acid, tartaric acid) and sodium bicarbonate, which release carbon dioxide when dissolved in water.

D. Statement About Warnings

Mandating warnings in an OTC drug monograph does not require a finding that any or all of the OTC drug products covered by the monograph actually caused an adverse event, and FDA does not so find. Nor does FDA's requirement of warnings repudiate the prior OTC drug monographs and monograph rulemakings under which the affected drug products have been lawfully marketed. Rather, as a consumer protection agency, FDA has determined that warnings are necessary to ensure that these OTC drug products continue to be safe and effective for their labeled indications under ordinary conditions of use as those terms are defined in the Federal Food, Drug, and Cosmetic Act. This judgment balances the benefits of these drug products against their potential risks. (See 21 CFR 330.10(a).)

FDA's decision to act in this instance need not meet the standard of proof required to prevail in a private tort action (*Glastetter* v. *Novartis Pharmaceuticals Corp.*, 252 F.3d 986, 991 (8th Cir. 2001)). To mandate warnings, or take similar regulatory action, FDA need not show, nor do we allege, actual causation. For an expanded discussion of case law supporting FDA's authority to require such warnings, see Labeling of Diphenhydramine-Containing Drug Products for Over-the-Counter Human Use, Final Rule, 67 FR 72555 (December 6, 2002).

E. USP Monograph

FDA's policy is that for an active ingredient to be included in an OTC drug FM, it is necessary to have publicly available chemical information that can be used by all manufacturers to determine that the ingredient is appropriate for use in their products. (See the **Federal Register** of April 3, 1989 (54 FR 13480 at 13486), and June 20, 1990 (55 FR 25204 at 25215).) Because phenylephrine bitartrate is not currently standardized and characterized for quality and purity in the official compendium, i.e., the United States Pharmacopoeia (USP)-National Formulary (NF), it will not be included in the FM until such information is available. A proposed compendial monograph for phenylephrine bitartrate was published in the *Pharmacopeial Forum* for May-June 2004 (Ref. 4). When a final compendial monograph is published in the USP-NF, FDA intends to finalize its proposal to include phenylephrine bitartrate in an effervescent tablet in the FM. Interim marketing of phenylephrine bitartrate in an effervescent tablet before an amendment to include this ingredient in the FM is finalized is not allowed and may subject any such products to regulatory action.

V. Analysis of Impacts

FDA has examined the impacts of this proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if the rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes and assessment of anticipated costs and benefits, before proposing ''any rule that

includes any Federal mandate that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by private sector, of $100,000,000 (adjusted annually for inflation) in any one year.''

FDA believes that this proposed rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. This proposed rule is not a significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order. As discussed in this section, FDA has determined that this proposed rule, if finalized, will not have a significant economic impact on a substantial number of small entities. The Unfunded Mandates Reform Act of 1995 does not require FDA to prepare a statement of costs and benefits for this proposed rule, because the proposed rule is not expected to result in any 1-year expenditure that would exceed $100 million adjusted for inflation. The current inflation adjusted statutory threshold is about $110 million.

The purpose of this proposed rule is to include phenylephrine bitartrate in the monograph for OTC nasal decongestant drug products. This proposal, when finalized, would allow manufacturers who market products containing this ingredient in foreign countries and manufacturers who would like to market products containing this ingredient in the United States to enter the market place under the OTC drug monograph instead of a new drug application (NDA). Cost savings will occur from marketing without an NDA.

Marketing a new OTC drug product containing phenylephrine bitartrate is optional for any interested manufacturer. The costs would involve the standard startup costs associated with marketing any new product under an OTC drug monograph. Manufacturers will not incur any costs determining how to state the product's labeling because the monograph amendment (and any eventual final rule) will provide that information. Any final rule that issues based on this proposal will not be expected to require any new reporting and recordkeeping activities. Therefore, no additional professional skills would be needed.

FDA considered but rejected several alternatives: (1) Not including phenylephrine bitartrate in the monograph, (2) allowing other combinations, and (3) allowing interim marketing. FDA rejected the first alternative because it considers the data presented supportive of monograph status. FDA rejected the second alternative because it has no data to support other combinations at this time. FDA rejected the third alternative because there currently is no USP monograph for this ingredient. FDA considers it inappropriate to allow interim marketing until there are uniform standards for the ingredient in an official compendial monograph that all manufacturers can follow, and FDA publishes a notice in the **Federal Register** to allow interim marketing to begin.

This analysis shows that FDA has considered the burden to small entities. FDA does not consider an exemption for small entities necessary because those manufacturers can enter the market place like larger entities anytime after this proposal is finalized. Therefore, FDA certifies that this proposed rule will not have a significant economic impact on a substantial number of small entities. No further analysis is required under the Regulatory Flexibility Act (5 U.S.C. 605(b)).

VI. Paperwork Reduction Act of 1995

FDA tentatively concludes that the proposed labeling requirements in this document are not subject to review by the Office of Management and Budget because they do not constitute a ''collection of information'' under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the monograph labeling is a ''public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public'' (5 CFR 1320.3(c)(2)).

VII. Environmental Impact

FDA has determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, FDA tentatively concludes that the proposed rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement has not been prepared.

IX. Comments

FDA is providing a period of 90 days for interested persons to submit written or electronic comments on the proposed rule to the Division of Dockets Management (see **ADDRESSES**). Three copies of all written comments are to be submitted. Individuals submitting written comments or anyone submitting electronic comments may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

X. Proposed Effective Date

FDA is proposing that any final rule that may issue based on this proposal become effective 30 days after its date of publication in the **Federal Register**.

XI. References

The following references are on display in the Division of Dockets Management (see **ADDRESSES**) under Docket No. 1976N–0052N and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Comment No. CP18.
2. Comment No. MM9.
3. FDA ''Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products–General Considerations,'' October 2000.
4. ''Phenylephrine Bitartrate'' in *Pharmacopeial Forum*, The United States Pharmacopeial Convention, Inc., Rockville, MD, 30(3):923–924, May-June 2004.

List of Subjects in 21 CFR Part 341

Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 341 be amended as follows:

PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTIASTHMATIC DRUG PRODUCTS FOR OVER–THE–COUNTER HUMAN USE

1. The authority citation for 21 CFR part 341 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

2. Section 341.3 is amended by adding paragraph (i) to read as follows:

§ 341.3 Definitions.

* * * * *

(i) *Effervescent tablet.* A tablet intended to be dissolved in water before

administration. It contains, in addition to the active ingredient(s), mixtures of acids (citric acid, tartaric acid) and sodium bicarbonate, which release carbon dioxide when dissolved in water.

3. Section 341.20 is amended by adding paragraph (a)(4) to read as follows:

§ 341.20 Nasal decongestant active ingredients.

* * * * *

(a) * * *

(4) Phenylephrine bitartrate in an effervescent tablet.

* * * * *

4. Section 341.40 is amended by revising paragraphs (b), (c), (e), (g), (i), (j), (m), (n), (p), (q), (r), (s), (t), (x), (y), (aa), and (bb) and by adding paragraph (cc) to read as follows:

§ 341.40 Permitted combinations of active ingredients.

* * * * *

(b) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), and (a)(3) provided that the product is labeled according to § 341.85.

(c) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), and (a)(3) and any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § 341.85.

* * * * *

(e) Any single antihistamine active ingredient identified in § 341.12(a) through (e) and (h) through (m) may be combined with any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(4) and any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), and (a)(3) provided that the product is labeled according to § 341.85(c)(4). Diphenhydramine citrate in §§ 341.12(f) and 341.14(a)(5) or diphenhydramine hydrochloride in §§ 341.12(g) and 341.14(a)(6) may be both the antihistamine and the antitussive active ingredient provided that the product is labeled according to § 341.70(a).

* * * * *

(g) Any single antihistamine active ingredient identified in § 341.12(a) through (e) or (h) through (m) may be combined with any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(4) and any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), or (a)(3) and any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § 341.85(c)(4). Diphenhydramine citrate in §§ 341.12(f) and 341.14(a)(5) or diphenhydramine hydrochloride in §§ 341.12(g) and 341.14(a)(6) may be both the antihistamine and the antitussive active ingredient provided that the product is labeled according to § 341.70(a).

* * * * *

(i) Any single oral antitussive active ingredient identified in § 341.14(a) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), or (a)(3) provided that the product is labeled according to § 341.85.

(j) Any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(4) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), or (a)(3) and any single expectorant active ingredient identified in § 341.18 provided that the product is labeled according to § 341.85.

* * * * *

(m) Any single oral antitussive active ingredient identified in § 341.14(a) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), or (a)(3) and any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § 341.85.

(n) Any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(4) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), or (a)(3) and any single expectorant active ingredient identified in § 341.18 and any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § 341.85.

* * * * *

(p) Any single expectorant active ingredient identified in § 341.18 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), or (a)(3) provided that the product is labeled according to § 341.85.

(q) Any single expectorant active ingredient identified in § 341.18 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), or (a)(3) and any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § 341.85.

(r) Any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), or (a)(3) may be combined with any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § 341.85.

(s) Any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), or (a)(3) may be combined with any generally recognized as safe and effective single oral anesthetic/analgesic active ingredient, or any combination of anesthetic/analgesic active ingredients provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § 341.85.

(t) Any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), or (a)(3) may be combined with any single antitussive active ingredient identified in § 341.14(a) or (b)(2) and any generally recognized as safe and effective single oral anesthetic/analgesic active ingredient, or any combination of anesthetic/analgesic active ingredients provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § 341.85. If the combination contains a topical antitussive, the product must be formulated in a solid dosage form to be dissolved in the mouth.

* * * * *

(x) Any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), or (a)(3) may be

combined with any generally recognized as safe and effective single oral demulcent active ingredient provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § 341.85.

(y) Any single antitussive active ingredient identified in § 341.14(a) or (b)(2) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), or (a)(3) and any generally recognized as safe and effective single oral demulcent active ingredient provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § 341.85. If the combination contains a topical antitussive, the product must be formulated in a solid dosage form to be dissolved in the mouth.

* * * * *

(aa) Any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), or (a)(3) may be combined with any generally recognized as safe and effective single oral anesthetic/analgesic active ingredient, or any combination of oral anesthetic/analgesic active ingredients and any generally recognized as safe and effective single oral demulcent active ingredient provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § 341.85.

(bb) Any single antitussive active ingredient identified in § 341.14(a) or (b)(2) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a)(1), (a)(2), or (a)(3) and any generally recognized as safe and effective single oral anesthetic/analgesic active ingredient, or any combination of anesthetic/analgesic active ingredients and any generally recognized as safe and effective single oral demulcent active ingredient provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § 341.85. If the combination contains a topical antitussive, the product must be formulated in a solid dosage form to be dissolved in the mouth.

(cc) Phenylephrine bitartrate identified in § 341.20(a)(4) may be combined with chlorpheniramine maleate identified in § 341.12(c) and aspirin provided the product is available only in an effervescent tablet and provided that the product is labeled according to § 341.85.

5. Section 341.80 is amended by revising the headings in paragraphs (c)(1)(i) and (c)(1)(ii), and by adding paragraph (d)(1)(iii) to read as follows:

§ 341.80 Labeling of nasal decongestant drug products.

* * * * *

(c) * * *

(1) *Oral nasal decongestants*—(i) *For products containing phenylephrine hydrochloride, pseudoephedrine hydrochloride, pseudoephedrine sulfate, or phenylephrine bitartrate identified in § 341.20(a)(1) through (a)(4) when labeled for adults.* * * *

* * * * *

(ii) *For products containing phenylephrine hydrochloride, pseudoephedrine hydrochloride, pseudoephedrine sulfate, or phenylephrine bitartrate identified in § 341.20(a)(1) through (a)(4) when labeled for children under 12 years of age.* * * *

* * * * *

(d) * * *

(1) * * *

(iii) *For products containing phenylephrine bitartrate identified in § 341.20(a)(4).* Include information on the number of dosage units and the quantity of water the dosage units are to be dissolved in prior to administration as shown in the following table:

Age[1]	Dose[1]
adults and children 12 years of age and over	15.6 milligrams every 4 hours not to exceed 62.4 milligrams in 24 hours
children 6 to under 12 years of age	7.8 milligrams every 4 hours not to exceed 31.2 milligrams in 24 hours
children under 6 years of age	ask a doctor

[1] Headings are not required to appear in the product's labeling.

* * * * *

6. Section 341.85 is amended by revising the headings in paragraphs (a)(1), (b)(1), (b)(2), (b)(3), and (c)(3).

§ 341.85 Labeling of permitted combinations of active ingredients.

* * * * *

(a) * * *

(1) *For permitted combinations identified in § 341.40(a), (c), (f), (g), (l), (m), (n), (o), (q), (r), and (cc) containing an analgesic-antipyretic active ingredient.* * * *

* * * * *

(b) * * *

(1) *For permitted combinations containing an analgesic-antipyretic active ingredient identified in § 341.40(a), (c), (f), (g), (l), (m), (n), (o), (q), (r), and (cc) when labeled for relief of general cough-cold symptoms and/or the common cold.* * * *

* * * * *

(2) *For permitted combinations containing an analgesic-antipyretic active ingredient identified in § 341.40(a), (c), (f), (g), (m), (q), (r), and (cc) when labeled for relief of hay fever/allergic rhinitis and/or sinusitis symptoms.* * * *

* * * * *

(3) *For permitted combinations containing an oral analgesic-antipyretic active ingredient identified in § 341.40(a), (c), (f), (g), (m), (q), (r), and (cc) when labeled for relief of general cough-cold symptoms and/or the common cold and for relief of hay fever/allergic rhinitis and/or sinusitis symptoms.* * * *

* * * * *

(c) * * *

(3) *For permitted combinations containing a nasal decongestant and an analgesic-antipyretic identified in § 341.40(c), (g), (m), (n), (q), (r), and (cc).*
* * *

* * * * *

Dated: October 26, 2004.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 04–24423 Filed 11–1–04; 8:45 am]

BILLING CODE 4160–01–S

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 63

[GA–112L–2004–1–FRL–7832–8]

Approval of Section 112(l) Authority for Hazardous Air Pollutants; Equivalency by Permit Provisions; National Emission Standards for Hazardous Air Pollutants From the Pulp and Paper Industry; State of Georgia

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: Pursuant to section 112(l) of the Clean Air Act (CAA), the Georgia Environmental Protection Division (GEPD) requested approval to implement and enforce State permit terms and conditions that substitute for the National Emission Standards for Hazardous Air Pollutants from the Pulp and Paper Industry. In the Rules section of this **Federal Register**, EPA is granting GEPD the authority to implement and enforce alternative requirements in the form of title V permit terms and conditions after EPA has approved the State's alternative requirements. A detailed rationale for this approval is set forth in the direct final rule. If no significant, or adverse comments are received, no further activity is contemplated. If EPA receives significant, or adverse comments, the direct final rule will be withdrawn and all public comments received will be addressed in a subsequent final rule based on this rule. The EPA will not institute a second comment period on this document. Any parties interested in commenting on this document should do so at this time.

DATES: Written comments must be received on or before November 23, 2004.

ADDRESSES: Comments may be submitted by mail to: Lee Page, Air Toxics Assessment and Implementation Section, Air Toxics and Monitoring Branch, Air, Pesticides and Toxics Management Division; U.S. Environmental Protection Agency Region 4; 61 Forsyth Street, SW., Atlanta, Georgia 30303–8960. Duplicate copies of all comments must also be submitted to Ron C. Methier, Chief, Air Protection Branch, Georgia Environmental Protection Division, 4244 International Parkway, Suite 120, Atlanta, Georgia 30354. Comments may also be submitted electronically, or through hand delivery/courier. Please follow the detailed instructions described in the direct final rule, **SUPPLEMENTARY INFORMATION** section [part (I)(B)(1)(i) through (iii)] which is published in the Rules section of this **Federal Register**.

FOR FURTHER INFORMATION CONTACT: Lee Page, Air Toxics Assessment and Implementation Section, Air Toxics and Monitoring Branch, Air, Pesticides and Toxics Management Division, Region 4, U.S. Environmental Protection Agency, 61 Forsyth Street, SW., Atlanta, Georgia 30303–8960. The telephone number is (404) 562–9141. Mr. Page can also be reached via electronic mail at *page.lee@epa.gov*.

SUPPLEMENTARY INFORMATION: For additional information see the direct final rule which is published in the Rules section of this **Federal Register**.

Dated: October 19, 2004.

J.I. Palmer, Jr.,

Regional Administrator, Region 4.

[FR Doc. 04–24410 Filed 11–1–04; 8:45 am]

BILLING CODE 6560–50–P

FEDERAL COMMUNICATIONS COMMISSION

47 CFR Part 27

[WT Docket No. 04–356; WT Docket No. 02–353; FCC 04–218]

Service Rules for Advanced Wireless Services in the 1915–1920 MHz, 1995–2000 MHz, 2175–2180 MHz and 1.7 GHz and 2.1 GHz Bands

AGENCY: Federal Communications Commission.

ACTION: Proposed rule.

SUMMARY: In connection with a decision to provide additional twenty megahertz of spectrum that can be used to offer a variety of broadband and advanced wireless services (AWS), potentially including ''third generation'' (3G) wireless services, the Commission ask for public comment on licensing, technical, and operational rules to govern the use of the 1915–1920 MHz, 1995–2000 MHz, and 2020–2025 MHz and 2175–2180 MHz bands designated for AWS. The Commission announced its desire to provide licensees of this spectrum with flexibility to provide any fixed or mobile service consistent with the technical parameters of allocation.

DATES: Comments are due on or before November 23, 2004, and reply comments are due on or before January 7, 2005. Written comments on the Paperwork Reduction Act proposed information collection requirements must be submitted by the public, Office of Management and Budget (OMB), and other interested parties on or before November 23, 2004.

ADDRESSES: In addition to filing comments with the Secretary, a copy of any comments on the Paperwork Reduction Act information collection requirements contained herein should be submitted to Judith B. Herman, Federal Communications Commission, Room 1–C804, 445 12th Street, SW., Washington, DC 20554, or via the Internet to *Judith-B.Herman@fcc.gov,* and to Kristy L. LaLonde, OMB Desk Officer, Room 10234 NEOB, 725 17th Street, NW., Washington, DC 20503 via the Internet to *Kristy_L.LaLonde@omb.eop.gov,* or via fax at 202–395–5167.

FOR FURTHER INFORMATION CONTACT: Peter Corea at 202–418–2487. For additional information concerning the Paperwork Reduction Act information collection requirements contained in this document, contact Judith B. Herman at 202–418–0214, or via Internet at *Judith-B.Herman@fcc.gov.*

SUPPLEMENTARY INFORMATION: This document contains proposed information collection requirements. The Commission, as part of its continuing effort to reduce paperwork burdens, invites the general public and the Office of Management and Budget (OMB) to comment on the information collection requirements contained in this document, as required by the Paperwork Reduction Act of 1995, Public Law 104–13. Public and agency comments are due on or before November 23, 2004. Comments should address: (a) Whether the proposed collection of information is necessary for the proper performance of the functions of the Commission, including whether the information shall have practical utility; (b) the accuracy of the Commission's burden estimates; (c) ways to enhance the quality, utility, and clarity of the information collected; and (d) ways to minimize the burden of the collection of information on the respondents, including the use of automated collection techniques or other forms of information technology. In addition, pursuant to the Small

The Class E airspace areas designated as 700/1,200 ft. transition areas are published in paragraph 6005 of FAA Order 7400.9N, *Airspace Designations and Reporting Points*, dated September 1, 2005, and effective September 15, 2005, which is incorporated by reference in 14 CFR 71.1. The Class E airspace designation listed in this document will be published subsequently in the Order.

The Rule

This amendment to 14 CFR part 71 revises Class E airspace at the Adak Airport, Alaska. This Class E airspace is revised to accommodate aircraft executing one new special SIAP and one new DP, and will be depicted on aeronautical charts for pilot reference. The intended effect of this rule is to provide adequate controlled airspace for Instrument Flight Rule (IFR) operations at the Adak Airport, Adak, Alaska.

The FAA has determined that this regulation only involves an established body of technical regulations for which frequent and routine amendments are necessary to keep them operationally current. It, therefore—(1) is not a ''significant regulatory action'' under Executive Order 12866; (2) is not a ''significant rule'' under DOT Regulatory Policies and Procedures (44 FR 11034; February 26, 1979); and (3) does not warrant preparation of a regulatory evaluation as the anticipated impact is so minimal. Since this is a routine matter that will only affect air traffic procedures and air navigation, it is certified that this rule will not have a significant economic impact on a substantial number of small entities under the criteria of the Regulatory Flexibility Act.

The FAA's authority to issue rules regarding aviation safety is found in Title 49 of the United States Code. Subtitle 1, section 106 describes the authority of the FAA Administrator. Subtitle VII, Aviation Programs, describes in more detail the scope of the agency's authority.

This rulemaking is promulgated under the authority described in subtitle VII, part A, subpart 1, section 40103, Sovereignty and use of airspace. Under that section, the FAA is charged with prescribing regulations to ensure the safe and efficient use of the navigable airspace. This regulation is within the scope of that authority because it creates Class E airspace sufficient in size to contain aircraft executing instrument procedures for the Adak Airport and represents the FAA's continuing effort to safely and efficiently use the navigable airspace.

List of Subjects in 14 CFR Part 71

Airspace, Incorporation by reference, Navigation (air).

Adoption of the Amendment

■ In consideration of the foregoing, the Federal Aviation Administration amends 14 CFR part 71 as follows:

PART 71—DESIGNATION OF CLASS A, CLASS B, CLASS C, CLASS D, AND CLASS E AIRSPACE AREAS; AIRWAYS; ROUTES; AND REPORTING POINTS

■ 1. The authority citation for 14 CFR part 71 continues to read as follows:

Authority: 49 U.S.C. 106(g), 40103, 40113, 40120; E.O. 10854, 24 FR 9565, 3 CFR 1959–1963 Comp., p. 389.

§ 71.1 [Amended]

■ 2. The incorporation by reference in 14 CFR 71.1 of Federal Aviation Administration Order 7400.9N, *Airspace Designations and Reporting Points*, dated September 1, 2005, and effective September 15, 2005, is amended as follows:

* * * * *

Paragraph 6005 Class E airspace extending upward from 700 feet or more above the surface of the earth.

* * * * *

AAL AK E5 Adak, AK [Revised]

Adak Airport, AK

(Lat. 51°52′41″ N., long. 176°38′46″ W.)

Mount Moffett NDB

(Lat. 51°52′19″ N., long. 176°40′34″ W.)

That airspace extending upward from 700 feet above the surface within a 7-mile radius of Adak Airport and within 5.2 miles northwest and 4.2 miles southeast of the 060° bearing of the Mount Moffett NDB extending from the 7-mile radius to 11.5 miles northeast of the Adak Airport; and that airspace extending upward from 1,200 feet above the surface within an 11-mile radius of the Adak Airport, and within 16 miles of the Adak Airport extending clockwise from the 033° bearing to the 081° bearing of the Mount Moffett NDB.

* * * * *

Issued in Anchorage, AK, on July 24, 2006.

Anthony M. Wylie,

Director, Alaska Flight Service Information Office.

[FR Doc. E6–12282 Filed 7–31–06; 8:45 am]

BILLING CODE 4910–13–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 341

[Docket No. 1976N–0052N] (formerly 76N–052N)

RIN 0910–AF34

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Amendment of Monograph for OTC Nasal Decongestant Drug Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule to amend the final monograph (FM) for over-the-counter (OTC) nasal decongestant drug products (drug products used to relieve nasal congestion due to a cold, hay fever, or other upper respiratory allergies) to add phenylephrine bitartrate (PEB), both individually and in combination drug products in an effervescent dosage form, as generally recognized as safe and effective (GRASE). An effervescent dosage form is intended to be dissolved in water before taking by mouth. This final rule is part of FDA's ongoing review of OTC drug products.

DATES: *Effective Date*: This rule is effective August 31, 2006.

FOR FURTHER INFORMATION CONTACT: Michael T. Benson, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 5484, Silver Spring, MD 20993, 301–796–2090.

SUPPLEMENTARY INFORMATION:

I. Background

A. Advance Notice of Proposed Rulemaking (ANPR)

1. OTC Cough-Cold Drug Products

In the **Federal Register** of September 9, 1976 (41 FR 38312), FDA published the report of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (Cough-Cold Panel). That Panel reviewed oral and topical nasal decongestant drug products and found several active ingredients, including phenylephrine hydrochloride (PEH), to be safe and effective ingredients for OTC use (41 FR 38312 at 38399 and 38400). The Cough-Cold Panel did not evaluate PEB.

2. OTC Oral Health Care Drug Products

In the **Federal Register** of May 25, 1982 (47 FR 22760), FDA published the report of the Advisory Review Panel on OTC Oral Cavity Drug Products (Oral Cavity Panel). That Panel reviewed the safety and effectiveness of two oral nasal decongestant ingredients, PEH and phenylpropanolamine hydrochloride (both in lozenge form for topical use), and classified these ingredients as Category III (more effectiveness data needed) (47 FR 22760 at 22911 through 22914). The Oral Cavity Panel did not evaluate PEB.

B. Tentative Final Monograph (TFM)

1. OTC Cough-Cold Drug Product

In the **Federal Register** of January 15, 1985 (50 FR 2220), FDA published the TFM for OTC nasal decongestant drug products. The TFM proposed PEH as a monograph ingredient, but PEB was not addressed due to lack of available data.

2. OTC Oral Health Care Drug Products

In the **Federal Register** of January 27, 1988 (53 FR 2436), FDA published the TFM for OTC oral health care (anesthetic/analgesic, astringent, debriding agent/oral wound cleanser, and demulcent) drug products. FDA referred the data on the oral nasal decongestant ingredients PEH and phenylpropanolamine hydrochloride in lozenge form for topical use to the rulemaking for OTC nasal decongestant drug products, because that was the primary rulemaking for these ingredients (53 FR 2436 at 2448 and 2449).

C. Final Monograph (FM) OTC Cough-Cold Drug Products

In the **Federal Register** of August 23, 1994 (59 FR 43386), FDA published the FM for OTC nasal decongestant drug products. The monograph included PEH as GRASE for oral and topical use as a nasal decongestant (21 CFR 341.20(a)(1) and (b)(8)). The monograph did not specify specific oral dosage forms. FDA acknowledged that PEB was submitted as an oral nasal decongestant active ingredient in an effervescent combination tablet for OTC use. FDA noted that PEB was not reviewed by the Cough-Cold Panel, or included in its report, and was not addressed in the FM for OTC nasal decongestant drug products (59 FR 43386 at 43394 and 43395). FDA reviewed data on PEB submitted in a comment and concluded that the data were inadequate to demonstrate the safety and effectiveness of PEB in an effervescent dosage form as an OTC oral nasal decongestant ingredient. Consequently, this ingredient was not included in the FM.

On March 20, 2002, a manufacturer submitted a citizen petition to amend the OTC nasal decongestant FM to include the ingredient PEB in an effervescent tablet as GRASE for use as a single ingredient or in combination with any monograph cough-cold active ingredient. The petition included:

- Domestic and international marketing experience to meet FDA's material time and extent criteria for inclusion in an OTC drug monograph (see 21 CFR 330.14)
- In vitro and in vivo studies to demonstrate comparability of PEB with PEH, an approved monograph active ingredient
- A proposal that PEB would provide consumers with greater choice in combination nasal decongestant/analgesic cough-cold formulations

In the **Federal Register** of November 2, 2004 (69 FR 63482), FDA published a proposed rule to amend the FM for OTC nasal decongestant products to add PEB in an effervescent tablet as a single ingredient or in combination with aspirin and chlorpheniramine maleate. A drug manufacturer and an individual submitted comments, which included several issues that are discussed in section II of this document.

II. The Agency's Conclusion on the Comments

(Comment 1) One comment asked FDA to expand the definition of an effervescent dosage form. FDA had proposed the following definition for an effervescent tablet: ''A tablet intended to be dissolved in water before administration. It contains, in addition to the active ingredient(s), mixtures of acids (citric acid, tartaric acid) and sodium bicarbonate, which releases carbon dioxide when dissolved in water.''

The comment requested that FDA revise the proposed definition of effervescent tablet to permit additional inactive ingredients, claiming that its suggested revision would provide greater formulation flexibility. The comment based its revised definition upon definitions from pharmaceutical texts and reference books, including the United States Pharmacopeia (U.S.P.), the British/European Pharmacopeia (BP/EP), and other pharmacopeial individual monographs. The comment requested that FDA revise the definition of effervescent tablet as follows: ''A tablet intended to be dissolved or dispersed in water before administration. It generally contains, in addition to the active ingredient(s), mixtures of acids/acid salts (citric acid, tartaric acid, malic acid, or any other suitable acid or acid anhydride), which release carbon dioxide when mixed with water. Occasionally, the active ingredient itself could act as the acid or alkali metal compound necessary for effervescent reaction.''

FDA declines the request to revise the definition of effervescent tablet to permit additional inactive ingredients, but is expanding the definition in a different manner to provide manufacturers greater formulation flexibility. FDA's definition in the OTC nasal decongestant FM is substantially the same as the definitions for effervescent tablets in the U.S.P. (Ref. 1) and for effervescent tablets and granules in the FDA Center for Drug Evaluation and Research (CDER) Data Standards Manual (Ref. 2). All of these definitions describe a dosage form that contains citric acid, tartaric acid, and sodium bicarbonate as inactive ingredients to produce the effervescence, and the product releases gas (carbon dioxide) when added to water.

FDA is not revising the definition in the manner suggested by the comment because the agency has concerns about the comment's proposed use of the term ''any other suitable acid or acid anhydride.'' This term is not sufficiently specific to ensure consistency with the current regulatory requirements for inactive ingredients. Under § 330.1(e) (21 CFR 330.1(e)), a product is required to contain only suitable inactive ingredients that meet certain criteria. These inactive ingredients must be safe in the amounts administered and must not interfere with the effectiveness of the preparation or with suitable tests or assays to determine if the product meets its professed standards of identity, strength, quality, and purity. The comment did not submit data to demonstrate that the additional inactive ingredients it requests are safe in the amounts administered or that they do not interfere with the effectiveness of the preparation or with suitable tests or assays. FDA is not aware of any such data for effervescent dosage forms that contain PEB. FDA is also not aware of PEB as the active ingredient in these products acting as ''the acid or alkali metal compound necessary for effervescent reaction.'' Accordingly, FDA is not adding this requested information to the definition at this time.

Interested parties should contact U.S.P. for any change in the compendial definition of an effervescent tablet that would apply to all such products. The definition in § 341.3(i) applies only to products containing PEB covered by this FM. Interested parties who wish to

include a PEB effervescent dosage form that contains different inactive ingredients than those listed in the definition in this FM may provide FDA specific data on such a product

FDA is expanding the definition of ''effervescent tablet'' by replacing ''effervescent tablet'' in § 341.3(i) of the proposed rule with ''effervescent dosage form'' in this final rule. We are making this change to provide greater formulation flexibility to permit other effervescent dosage forms (e.g., granules and powders) to be marketed. The FDA CDER Data Standards Manual (Ref. 2) defines an effervescent granule as ''a small particle or grain containing a medicinal agent in a dry mixture * * *.'' The pharmacokinetic data provided for the PEB effervescent tablet dosage form would also support use of an effervescent granule or powder dosage form, based on the smaller particle size of these dosage forms. Accordingly, the definition in § 341.3(i) now reads: ''*Effervescent dosage form.* A dosage form intended to be dissolved in water before administration. It contains, in addition to the active ingredient(s), mixtures of acids (citric acid, tartaric acid) and sodium bicarbonate, which release carbon dioxide when dissolved in water.'' In conjunction with this change, we have also changed the proposed active ingredient description ''phenylephrine bitartrate effervescent tablet'' in § 341.20(a)(4) to ''phenylephrine bitartrate effervescent dosage form'' in this FM.

(Comment 2) One comment requested FDA to allow PEB as an oral nasal decongestant in all combination products containing an oral nasal decongestant when formulated as an effervescent tablet and labeled in accordance with 21 CFR 341.80 and 21 CFR 341.85. The comment contended that PEH is included as a GRASE oral nasal decongestant ingredient in the monograph for OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products and is included in 17 permitted combinations. The comment further stated that FDA acknowledged in the proposed rule that both phenylephrine salts (bitartrate and hydrochloride) have similar safety and efficacy profiles, and could be used in effervescent tablets interchangeably without any clinically significant impact on the performance of the formulations studied. The comment provided in-vitro data demonstrating comparable recovery of the active ingredient following dissolution in various solution media of effervescent tablets formulated with either PEH or PEB, in the presence or absence of other common cough/cold active ingredients.

FDA agrees with the comment. In the **Federal Register** of January 15, 1985 (50 FR 2220), FDA affirmed the Cough-Cold Panel recommendations for numerous combinations containing an oral nasal decongestant and other active ingredients. PEH was one of those active ingredients. In the proposed rule of the current rulemaking (69 FR 63482 at 63485, November 2, 2004), FDA acknowledged that the two phenylephrine salts in effervescent tablets could be used interchangeably. The similarity in the rate and extent of absorption of PEH and PEB in the effervescent tablets allows FDA to conclude that the bioavailability of the phenylephrine salts in the effervescent tablets is comparable (69 FR 63482, November 2, 2004). With regard to PEB and other combinations:

- PEH is similarly bioavailable to PEB, as stated previously, and in-vitro dissolution data demonstrate that recovery of phenylephrine from formulations of either salt is virtually indistinguishable (PEH v PEB). FDA believes that PEB would have also been among the ingredients recommended for inclusion in the same combinations as PEH, had the Cough-Cold Panel considered that ingredient. Accordingly, FDA is including PEB in an effervescent dosage form as a permitted active ingredient as follows:
- In the same types of combination products as the other oral nasal decongestant active ingredients under §§ 341.40 (b), (c), (e), (g), (i), (j), (m), (n), (p), (q), (r), (s), (t), (x), (y), (aa), and (bb),
- With labeling for combination products under § 341.85 (b)(1), (b)(2), (b)(3), and (c)(3).

(Comment 3) One comment contended that FDA should not approve PEB for OTC use until an official compendium exists to define the quality and purity of its effervescent dosage form. FDA does not agree with the comment's suggestion. PEB as a drug substance became official in the U.S.P. on August 1, 2005 (Ref. 3). FDA's regulation in 21 CFR 330.14(i) sets forth criteria and procedures for classifying OTC drugs as GRASE and not misbranded. It states that ''any active ingredient or botanical drug substance included in a final OTC drug monograph * * * must be recognized in an official USP-NF drug monograph that sets forth its standards of identity, strength, quality, and purity.'' While FDA's regulation mentions a U.S.P.–N.F. drug monograph for the active ingredient, it does not also require a U.S.P.–N.F. drug monograph for the active ingredient in a specific dosage form. Accordingly, FDA concludes that a U.S.P. compendial monograph for the PEB drug substance is a sufficient basis for including PEB as an active ingredient in an effervescent tablet or other effervescent dosage form in the FM for OTC nasal decongestant drug products.

III. Submission of Pharmacokinetic Data for Other Solid Dosage Forms of PEB

FDA notes in the proposed rule that the rate and extent of absorption after the first dose of PEB capsules are not similar to PEH capsules. FDA is willing to consider pharmacokinetic data in support of other PEB solid dosage forms (e.g., capsule, or noneffervescent tablet, granule, or powder) and invites interested persons to submit such data in the form of a petition under 21 CFR 10.30 to amend the monograph for OTC nasal decongestant drug products.

IV. Labeling Change from the Proposed Rule

At the time of the proposed rule, sinusitis would have been a permitted indication for OTC combination drug products that include PEB in an effervescent dosage form as an oral nasal decongestant. Subsequently, FDA revised the labeling for these products. In the **Federal Register** of October 11, 2005 (70 FR 58974), FDA published a final rule to eliminate the term ''sinusitis'' from the labeling of OTC nasal decongestant drug products. Accordingly, FDA has revised the introductory language of §§ 341.85(b)(2) and (b)(3) of the proposed rule to replace the term ''sinusitis'' with ''nasal congestion.'' Sections 341.85(b)(2) and (b)(3) of the final rule now read as follows:

''§ 341.85 *Labeling of permitted combinations of active ingredients.*

(b)(2) *For permitted combinations containing an analgesic-antipyretic active ingredient * * * when labeled for relief of hay fever/allergic rhinitis and/or nasal congestion symptoms.*

(b)(3) *For permitted combinations containing an oral analgesic-antipyretic active ingredient * * * when labeled for relief of general cough-cold symptoms and/or the common cold and for relief of hay fever/allergic rhinitis and/or nasal congestion symptoms.*''

V. Summary of Agency Changes

1. FDA is changing the definition of ''effervescent tablet'' in § 341.3(i) to ''effervescent dosage form.'' In conjunction with this change, FDA is changing the active ingredient description in § 341.20(a)(4) from ''Phenylephrine bitartrate in an effervescent tablet'' to ''Phenylephrine bitartrate in an effervescent dosage

form'' (see section II, comment 1 of this document).

2. In the proposed rule, FDA proposed to amend § 341.40(b), (c), (e), (g), (i), (j), (m), (n), (p), (q), (r), (s), (t), (x), (y), (aa), and (bb) to exclude PEB in § 341.20(a)(4). Now that FDA is allowing PEB in all of these combinations, there is no need to amend these paragraphs because the existing language therein already refers to all nasal decongestant active ingredients in § 341.20(a).

3. FDA is eliminating proposed § 341.40 (cc) because the combination is now covered by § 341.40(c). With the elimination of proposed § 341.40(cc), the proposed amendments of the headings in § 341.85(a)(1), (b)(1), (b)(2), (b)(3), and (c)(3) to add § 341.40(cc) are no longer needed and are withdrawn. However, the headings in § 314.85(b)(2) and (b)(3) are being revised as discussed in section IV of this document.

VI. Analysis of Impacts

FDA has examined the impacts of this final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if the rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement of anticipated costs and benefits before enacting any rule that may result in an expenditure in any one year by state, local, and tribal governments, in the aggregate, or by private sector, of $100 million (adjusted annually for inflation).

FDA believes that this final rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. This final rule is not a significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order. As discussed in this section, FDA has determined that this final rule will not have a significant economic impact on a substantial number of small entities. The Unfunded Mandates Reform Act of 1995 does not require FDA to prepare a statement of costs and benefits for this final rule, because the final rule is not expected to result in any 1-year expenditure that would exceed $100 million adjusted for inflation. The current threshold after adjustment for inflation is $115 million, using the most current (2003) Implicit Price Deflator for the Gross Domestic Product.

The purpose of this final rule is to include PEB in the monograph for OTC nasal decongestant drug products. This final rule will allow manufacturers who market products containing this ingredient in foreign countries and manufacturers who would like to market products containing this ingredient in the United States to enter the market place under the OTC drug monograph instead of a new drug application (NDA). Cost savings will occur from marketing without an NDA.

Marketing a new OTC drug product containing PEB is optional for any interested manufacturer. The costs would involve the standard startup costs associated with marketing any new product under an OTC drug monograph. Manufacturers will not incur any costs determining how to state the product's labeling because the monograph amendment provides that information. This final rule is not expected to require any new reporting and recordkeeping activities. Therefore, no additional professional skills will be needed.

FDA considered but rejected the option of not including PEB in the monograph because it considers the data presented supportive of monograph status. The ingredient became official in the U.S.P. on August 1, 2005 (Ref. 3).

This analysis shows that FDA has considered the burden to small entities. FDA does not consider an exemption for small entities necessary because those manufacturers can enter the market place like larger entities anytime after this FM becomes effective. Therefore, FDA certifies that this final rule will not have a significant economic impact on a substantial number of small entities. No further analysis is required under the Regulatory Flexibility Act (5 U.S.C. 605(b)).

VII. Paperwork Reduction Act of 1995

FDA concludes that the labeling requirements in this document are not subject to review by the Office of Management and Budget because they do not constitute a ''collection of information'' under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the monograph labeling is a ''public disclosure of information originally supplied by the Federal Government to the recipient for the purpose of disclosure to the public'' (5 CFR 1320.3(c)(2)).

VIII. Environmental Impact

FDA has determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule will have a preemptive effect on State law. Section 4(a) of the Executive order requires agencies to ''construe * * * a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute.'' Section 751 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 379r) is an express preemption provision. Section 751(a) of the act (21 U.S.C. 379r(a)) provides that: ''* * * no State or political subdivision of a State may establish or continue in effect any requirement— * * * (1) that relates to the regulation of a drug that is not subject to the requirements of section 503(b)(1) or 503(f)(1)(A); and (2) that is different from or in addition to, or that is otherwise not identical with, a requirement under this Act, the Poison Prevention Packaging Act of 1970 (15 U.S.C. 1471 *et seq.*), or the Fair Packaging and Labeling Act (15 U.S.C. 1451 *et seq.*).'' Currently, this provision operates to preempt States from imposing requirements related to the regulation of nonprescription drug products. (See Section 751(b) through (e) of the act for the scope of the express preemption provision, the exemption procedures, and the exceptions to the provision.) This final rule would add PEB, individually and in combination drug products when used in effervescent dosage form, to the FM for OTC nasal decongestant drug products. Although this final rule would have a preemptive effect, in that it would preclude States from promulgating requirements related to these PEB drug products that are different from or in addition to, or not otherwise identical with a requirement in the final rule, this preemptive effect is consistent with what Congress set forth in section 751 of the act. Section 751(a) of the act

displaces both State legislative requirements and State common law duties. We also note that even where the express preemption provision is not applicable, implied preemption may arise. See *Geier* v. *American Honda Co.*, 529 US 861 (2000).

FDA believes that the preemptive effect of the final rule would be consistent with Executive Order 13132. Section 4(e) of the Executive order provides that ''when an agency proposes to act through adjudication or rulemaking to preempt State law, the agency shall provide all affected State and local officials notice and an opportunity for appropriate participation in the proceedings.'' FDA provided the States with an opportunity for appropriate participation in this rulemaking when it sought input from all stakeholders through publication of the proposed rule in the **Federal Register** of November 2, 2004 (69 FR 63482). FDA received no comments from any States on the proposed rulemaking.

In addition, on June 19, 2006, FDA's Division of Federal and State Relations provided notice via fax and email transmission to elected officials of State governments and their representatives of national organizations. The notice provided the States with further opportunity for comment on the rule. It advised the States of the publication of the proposed rule and encouraged State and local governments to review the notice and to provide any comments to Docket No. 1976N–0052N, opened in the November 2, 2004, **Federal Register** notice, by a date 30 days from the date of the notice (i.e., by July 19, 2006), or to contact certain named individuals. FDA received no comments in response to this notice. The notice has been filed in Docket No. 1976N–0052N.

In conclusion, FDA believes that it has complied with all of the applicable requirements under the Executive order and has determined that the preemptive effects of this rule are consistent with Executive Order 13132.

X. Effective Date

This final rule becomes effective August 31, 2006.

XI. References

The following references are on display in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852 under Docket No. 1976N–0052N and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site address, but is not responsible for subsequent changes to the Web site after this document publishes in the **Federal Register**.)

1. *The United States Pharmacopeia 29–National Formulary 24*, The United States Pharmacopeial Convention, Inc., Rockville, MD, pp 3005, 2006.

2. *CDER Data Standards Manual* (see sections entitled ''Tablet Effervescent'' and ''Granule Effervescent'') at *http://www.fda.gov/cder/dsm/DRG/drg00201.htm*.

3. *The United States Pharmacopeia 28–National Formulary 23, Supplement 2*, The United States Pharmacopeial Convention, Inc., Rockville, MD, pp 3520, 2005.

List of Subjects in 21 CFR Part 341

Labeling, Over-the-counter drugs.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 341 is amended as follows:

PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTIASTHMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

■ 1. The authority citation for 21 CFR part 341 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

■ 2. Section 341.3 is amended by adding paragraph (i) to read as follows:

§ 341.3 Definitions.

* * * * *

(i) *Effervescent dosage form.* A dosage form intended to be dissolved in water before administration. It contains, in addition to the active ingredient(s), mixtures of acids (citric acid, tartaric acid) and sodium bicarbonate, which release carbon dioxide when dissolved in water.

■ 3. Section 341.20 is amended by adding paragraph (a) (4) to read as follows:

§ 341.20 Nasal decongestant active ingredients.

* * * * *

(a) * * *

(4) Phenylephrine bitartrate in an effervescent dosage form.

* * * * *

■ 4. Section 341.80 is amended by revising the headings in paragraphs (c)(1)(i) and (c)(1)(ii), and by adding paragraph (d)(1)(iii) to read as follows:

§ 341.80 Labeling of nasal decongestant drug products.

* * * * *

(c) * * *

(1) *Oral nasal decongestants*—(i) *For products containing phenylephrine hydrochloride, pseudoephedrine hydrochloride, pseudoephedrine sulfate, or phenylephrine bitartrate identified in § 341.20 (a)(1) through (a)(4) when labeled for adults.* * * *

* * * * *

(ii) *For products containing phenylephrine hydrochloride, pseudoephedrine hydrochloride, pseudoephedrine sulfate, or phenylephrine bitartrate identified in § 341.20 (a)(1) through (a)(4) when labeled for children under 12 years of age.* * * *

* * * * *

(d) * * *

(1) * * *

(iii) *For products containing phenylephrine bitartrate identified in § 341.20(a)(4).* Include information on the number of dosage units and the quantity of water the dosage units are to be dissolved in prior to administration as shown in the following table:

Age[1]	Dose[1]
Adults and children 12 years of age and over	15.6 milligrams every 4 hours not to exceed 62.4 milligrams in 24 hours
Children 6 to under 12 years of age	7.8 milligrams every 4 hours not to exceed 31.2 milligrams in 24 hours
Children under 6 years of age	Ask a doctor

[1]Headings are not required to appear in the product's labeling

* * * * *

■ 5. Section 341.85 is amended by revising the headings in paragraphs (b)(2) and (b)(3).

§ 341.85 Labeling of permitted combinations of active ingredients.

* * * * *

(b) * * *

(2) *For permitted combinations containing an analgesic-antipyretic active ingredient identified in § 341.40 (a), (c), (f), (g), (m), (q), and (r) when labeled for relief of hay fever/allergic rhinitis and/or nasal congestion symptoms.****

* * * * *

(3) *For permitted combinations containing an oral analgesic-antipyretic active ingredient identified in § 341.40 (a), (c), (f), (g), (m), (q), and (r) when labeled for relief of general cough-cold symptoms and/or the common cold and for relief of hay fever/allergic rhinitis and/or nasal congestion symptoms.****

* * * * *

Dated: July 24, 2006.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. E6–12265 Filed 7–31–06; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Part 1

[TD 9272]

RIN 1545–BE81

REMIC Residual Interests—Accounting for REMIC Net Income (Including Any Excess Inclusions) (Foreign Holders)

AGENCY: Internal Revenue Service (IRS), Treasury.

ACTION: Final and temporary regulations.

SUMMARY: This document contains temporary regulations relating to income that is associated with a residual interest in a Real Estate Mortgage Investment Conduit (REMIC) and that is allocated through certain entities to foreign persons who have invested in those entities. The regulations accelerate the time when income is recognized for withholding tax purposes to conform to the timing of income recognition for general income tax purposes. The foreign persons covered by these regulations include partners in domestic partnerships, shareholders of real estate investment trusts, shareholders of regulated investment companies, participants in common trust funds, and patrons of subchapter T cooperatives. These regulations are necessary to prevent inappropriate avoidance of current income tax liability by foreign persons to whom income from REMIC residual interests is allocated. The regulations clarify the timing of income under section 860G for purposes of determining a domestic partnership's responsibility under sections 1441 and 1442 for withholding tax with respect to a foreign partner's share of REMIC net income as a result of indirectly holding a residual interest. The regulations also provide that an excess inclusion is treated as income from sources within the United States. The text of the temporary regulations also serves as the text of the proposed regulations set forth in the notice of proposed rulemaking on this subject in the Proposed Rules section in this issue of the **Federal Register**.

DATES: *Effective Date:* These regulations are effective August 1, 2006.

Applicability Dates: For dates of applicability, see §§ 1.860A–1T(b)(5), 1.863–1T(f) and 1.1441–2T(f).

FOR FURTHER INFORMATION CONTACT: Dale Collinson, (202) 622–3900 (not a toll-free number).

Background and Explanation of Provisions

This document contains amendments to 26 CFR part 1 under sections 860A, 860G(b), 863, 1441, and 1442 of the Internal Revenue Code (Code). Under section 860C(a)(1), in general, a holder of a REMIC residual interest must take into account the holder's daily portion of the taxable income or net loss of the REMIC for each day of the taxable year on which the holder held the interest. Thus, a residual interest holder generally is taxable currently on the taxable income or net loss of the REMIC without regard to whether or when the REMIC makes distributions. Section 860G(b) provides an exception to this general rule in section 860C for the timing of income attributable to the ownership of a REMIC residual interest. Under this exception, for purposes of sections 871(a), 881, 1441, and 1442, if amounts are includible in the income of a holder of a REMIC residual interest that is a nonresident alien individual or a foreign corporation, the amounts are taken into account only when paid or distributed to the foreign holder, or when the interest is disposed of.

In its earlier years, a REMIC may accrue and recognize more taxable interest income from the mortgages that it holds than it accrues and deducts as interest on the regular interests that it has issued. This produces net income for the REMIC and thus for the holder of the REMIC's residual interest. Many REMICs are structured so that the REMIC uses all, or substantially all, of its cash flow to pay expenses and to pay principal and interest on regular interests (effectively using a portion of interest receipts to pay principal or other nondeductible items). Such a REMIC will make little or no distributions to the holders of the residual interest in the REMIC, and each holder will incur tax liabilities with respect to its share of the REMIC's net income in an amount that exceeds the holder's economic return.

In addition, all or substantially all of the income attributable to holding the residual interest will be subject to special rules relating to *excess inclusions*. To ensure that the income will be taxable in all events, these rules, among other things, prevent the use of net operating losses to offset the excess inclusions, see section 860E, and preclude any exemption from, or reduction in, applicable withholding taxes, see section 860G(b)(2). Residual interests that entitle the holder to little or no distributions are commonly referred to as *noneconomic* REMIC residual interests, and persons acquiring those interests receive an *inducement fee* for becoming the holder and undertaking the associated tax payment responsibilities. Taxable income that must be recognized in excess of the economic income for a period is often called *phantom income.* In the case of a REMIC, the early phantom income is generally offset by matching deductions (generally called *phantom losses*) in later periods.

Consistent with the Congressional purpose of ensuring that excess inclusions of REMICs be subject to tax, § 1.860E–1(c) of the Income Tax Regulations provides for disregarding transfers of noneconomic REMIC residual interests if a significant purpose of the transfer is avoiding assessment or collection of tax. In addition, § 1.860G–3(a)(1) provides, ''A transfer of a residual interest that has tax avoidance potential is disregarded for all Federal income tax purposes if the transferee is a foreign person.'' Section 1.860G–3(a)(2) provides, ''A residual interest has tax avoidance potential * * * unless, at the time of the transfer, the transferor reasonably expects that, for each excess inclusion, the REMIC will distribute to the transferee residual interest holder an amount that will equal at least 30 percent of the excess inclusion, and that each such amount will be distributed at or after the time at which the excess inclusion accrues and not later than the close of the calendar year following the calendar year of accrual.'' Accordingly, foreign persons are generally precluded from becoming the direct holders of noneconomic residual interests.

''Where necessary or appropriate to prevent the avoidance of tax imposed by [chapter 1 of the Code],'' section 860G(b) authorizes the adoption of regulations requiring REMIC net income inclusions of foreign holders of REMIC residual interests to be taken into account for purposes of sections 871(a), 881, 1441, and 1442 earlier than is provided in section 860G(b)(1). The legislative history of the Tax Reform Act of 1986 indicates that Congress intended that this regulatory authority may be exercised with respect to noneconomic residual interests. *See* 2 H.R. Rep. No. 841, 99th Cong., 2d Sess. II–236 (1986) (referring to residual interests that do ''not have significant value'').

The IRS and Treasury Department have become aware that noneconomic REMIC residual interests are being

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) "The recommended dose of this product contains about as much caffeine as a cup of coffee. Limit the use of caffeine-containing medications, foods, or beverages while taking this product because too much caffeine may cause nervousness, irritability, sleeplessness, and, occasionally, rapid heart beat."

(2) "For occasional use only. Not intended for use as a substitute for sleep. If fatigue or drowsiness persists or continues to recur, consult a" (select one of the following: "physician" or "doctor").

(3) "Do not give to children under 12 years of age."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions": Adults and children 12 years of age and over: Oral dosage is 100 to 200 milligrams not more often than every 3 to 4 hours.

PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTIASTHMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Subpart B—Active Ingredients

Subpart C—Labeling

AUTHORITY: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

EDITORIAL NOTE: Nomenclature changes to part 341 appear at 69 FR 13717, Mar. 24, 2004.

Subpart A—General Provisions

§ 341.1 Scope.

(a) An over-the-counter cold, cough, allergy, bronchodilator, or antiasthmatic drug product in a form suitable for oral, inhalant, or topical administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this part and each of the general conditions established in § 330.1.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21 unless otherwise noted.

[51 FR 35339, Oct. 2, 1986]

§ 341.3 Definitions.

As used in this part:

(a) *Bronchodilator drug.* A drug used to overcome spasms that cause narrowing of the bronchial air tubes, such as in the symptomatic treatment of the wheezing and shortness of breath of asthma.

(b) *Oral antitussive drug.* A drug that either is taken by mouth or is dissolved in the mouth in the form of a lozenge and acts systemically to relieve cough.

(c) *Topical antitussive drug.* A drug that relieves cough when inhaled after being applied topically to the throat or chest in the form of an ointment or from a steam vaporizer, or when dissolved in the mouth in the form of a lozenge for a local effect.

(d) *Expectorant drug.* A drug taken orally to promote or facilitate the removal of secretions from the respiratory airways.

(e) *Antihistamine drug.* A drug used for the relief of the symptoms of hay

fever and upper respiratory allergies (allergic rhinitis).

(f) *Oral nasal decongestant drug.* A drug that is taken by mouth and acts systemically to reduce nasal congestion caused by acute or chronic rhinitis.

(g) *Topical nasal decongestant drug.* A drug that when applied topically inside the nose, in the form of drops, jellies, or sprays, or when inhaled intranasally reduces nasal congestion caused by acute or chronic rhinitis.

(h) *Calibrated dropper.* A dropper calibrated such that the volume error incurred in measuring any liquid does not exceed 15 percent under normal use conditions.

(i) *Effervescent dosage form.* A dosage form intended to be dissolved in water before administration. It contains, in addition to the active ingredient(s), mixtures of acids (citric acid, tartaric acid) and sodium bicarbonate, which release carbon dioxide when dissolved in water.

[51 FR 35339, Oct. 2, 1986, as amended at 54 FR 8509, Feb. 28, 1989; 55 FR 40382, Oct. 3, 1990; 57 FR 58374, Dec. 9, 1992; 59 FR 43409, Aug. 23, 1994; 71 FR 43362, Aug. 1, 2006]

Subpart B—Active Ingredients

§ 341.12 Antihistamine active ingredients.

The active ingredient of the product consists of any of the following when used within the dosage limits established for each ingredient:

(a) Brompheniramine maleate.
(b) Chlorcyclizine hydrochloride.
(c) Chlorpheniramine maleate.
(d) Dexbrompheniramine maleate.
(e) Dexchlorpheniramine maleate.
(f) Diphenhydramine citrate.
(g) Diphenhydramine hydrochloride.
(h) Doxylamine succinate.
(i) Phenindamine tartrate.
(j) Pheniramine maleate.
(k) Pyrilamine maleate.
(l) Thonzylamine hydrochloride.
(m) Triprolidine hydrochloride.

[57 FR 58374, Dec. 9, 1992, as amended at 59 FR 4218, Jan. 28, 1994]

§ 341.14 Antitussive active ingredients.

The active ingredients of the product consist of any of the following when used within the dosage limits and in the dosage forms established for each ingredient in § 341.74(d):

(a) *Oral antitussives.* (1) Chlophedianol hydrochloride.

(2) *Codeine ingredients.* The following ingredients may be used only in combination in accordance with §§ 290.2 and 21 CFR 1308.15(c).

(i) Codeine.
(ii) Codeine phosphate.
(iii) Codeine sulfate.
(3) Dextromethorphan.
(4) Dextromethorphan hydrobromide.
(5) Diphenhydramine citrate.
(6) Diphenhydramine hydrochloride.
(b) *Topical antitussives.* (1) Camphor.
(2) Menthol.

[52 FR 30055, Aug. 12, 1987, as amended at 59 FR 29174, June 3, 1994; 67 FR 4907, Feb. 1, 2002]

§ 341.16 Bronchodilator active ingredients.

The active ingredients of the product consist of any of the following when used within the dosage limits established for each ingredient:

(a) Ephedrine.
(b) Ephedrine hydrochloride.
(c) Ephedrine sulfate.
(d) Epinephrine.
(e) Epinephrine bitartrate.
(f) Racephedrine hydrochloride.
(g) Racepinephrine hydrochloride.

[51 FR 35339, Oct. 2, 1986]

§ 341.18 Expectorant active ingredient.

The active ingredient of the product is guaifenesin when used within the dosage limits established in § 341.78(d).

[54 FR 8509, Feb. 28, 1989]

§ 341.20 Nasal decongestant active ingredients.

The active ingredient of the product consists of any of the following when used within the dosage limits and in the dosage forms established for each ingredient:

(a) *Oral nasal decongestants.* (1) Phenylephrine hydrochloride.
(2) Pseudoephedrine hydrochloride.
(3) Pseudoephedrine sulfate.
(4) Phenylephrine bitartrate in an effervescent dosage form.

(b) *Topical nasal decongestants.* (1) Levmetamfetamine.
(2) Ephedrine.
(3) Ephedrine hydrochloride.

(4) Ephedrine sulfate.
(5) [Reserved]
(6) Naphazoline hydrochloride.
(7) Oxymetazoline hydrochloride.
(8) Phenylephrine hydrochloride.
(9) Propylhexedrine.
(10) Xylometazoline hydrochloride.

[59 FR 43409, Aug. 23, 1994, as amended at 63 FR 40650, July 30, 1998; 71 FR 43362, Aug. 1, 2006]

§ 341.40 Permitted combinations of active ingredients.

The following combinations are permitted provided each active ingredient is present within the dosage limits established in parts 341, 343, and 356 of this chapter and the product is labeled in accordance with §§ 341.70 or 341.85:

(a) Any single antihistamine active ingredient identified in § 341.12 may be combined with any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § 341.85.

(b) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a) provided that the product is labeled according to § 341.85.

(c) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a) and any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § 341.85.

(d) Any single antihistamine active ingredient identified in § 341.12(a) through (e) and (h) through (m) may be combined with any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(4) provided that the product is labeled according to § 341.85(c)(4). Diphenhydramine citrate in §§ 341.12(f) and 341.14(a)(5) or diphenhydramine hydrochloride in §§ 341.12(g) and 341.14(a)(6) may be both the antihistamine and the antitussive active ingredient provided that the product is labeled according to § 341.70(a).

(e) Any single antihistamine active ingredient identified in § 341.12(a) through (e) and (h) through (m) may be combined with any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(4) and any single oral nasal decongestant active ingredient identified in § 341.20(a) provided that the product is labeled according to § 341.85(c)(4). Diphenhydramine citrate in §§ 341.12(f) and 341.14(a)(5) or diphenhydramine hydrochloride in §§ 341.12(g) and 341.14(a)(6) may be both the antihistamine and the antitussive active ingredient provided that the product is labeled according to § 341.70(a).

(f) Any single antihistamine active ingredient identified in § 341.12(a) through (e) and (h) through (m) may be combined with any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(4) and any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § 341.85(c)(4). Diphenhydramine citrate in §§ 341.12(f) and 341.14(a)(5) or diphenhydramine hydrochloride in §§ 341.12(g) and 341.14(a)(6) may be both the antihistamine and the antitussive active ingredient provided that the product is labeled according to § 341.70(a).

(g) Any single antihistamine active ingredient identified in § 341.12(a) through (e) and (h) through (m) may be combined with any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(4) and any single oral nasal decongestant active ingredient identified in § 341.20(a) and any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § 341.85(c)(4). Diphenhydramine citrate in §§ 341.12(f)

and 341.14(a)(5) or diphenhydramine hydrochloride in §§341.12(g) and 341.14(a)(6) may be both the antihistamine and the antitussive active ingredient provided that the product is labeled according to §341.70(a).

(h) Any single oral antitussive active ingredient identified in §341.14(a)(1) through (a)(4) may be combined with any single expectorant active ingredient identified in §341.18 provided that the product is labeled according to §341.85.

(i) Any single oral antitussive active ingredient identified in §341.14(a) may be combined with any single oral nasal decongestant active ingredient identified in §341.20(a) provided that the product is labeled according to §341.85.

(j) Any single oral antitussive active ingredient identified in §341.14(a)(1) through (a)(4) may be combined with any single oral nasal decongestant active ingredient identified in §341.20(a) and any single expectorant active ingredient identified in §341.18 provided that the product is labeled according to §341.85.

(k) Any single antitussive active ingredient identified in §341.14(a) or (b)(2) may be combined with any generally recognized as safe and effective single oral anesthetic/analgesic active ingredient, or any combination of anesthetic/analgesic active ingredients provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to §341.85. If the combination contains a topical antitussive, the product must be formulated in a solid dosage form to be dissolved in the mouth. Menthol in §341.14(b)(2) and part 356 of this chapter may be both the antitussive and the anesthetic/analgesic active ingredient provided that the product is labeled according to §341.70(b).

(l) Any single oral antitussive active ingredient identified in §341.14(a) may be combined with any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to §341.85.

(m) Any single oral antitussive active ingredient identified in §341.14(a) may be combined with any single oral nasal decongestant active ingredient identified in §341.20(a) and any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to §341.85.

(n) Any single oral antitussive active ingredient identified in §341.14(a)(1) through (a)(4) may be combined with any single oral nasal decongestant active ingredient identified in §341.20(a) and any single expectorant active ingredient identified in §341.18 and any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to §341.85.

(o) Any single expectorant active ingredient identified in §341.18 may be combined with any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to §341.85.

(p) Any single expectorant active ingredient identified in §341.18 may be combined with any single oral nasal decongestant active ingredient identified in §341.20(a) provided that the product is labeled according to §341.85.

(q) Any single expectorant active ingredient identified in §341.18 may be combined with any single oral nasal decongestant active ingredient identified in §341.20(a) and any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to §341.85.

(r) Any single oral nasal decongestant active ingredient identified in §341.20(a) may be combined with any

generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § 341.85.

(s) Any single oral nasal decongestant active ingredient identified in § 341.20(a) may be combined with any generally recognized as safe and effective single oral anesthetic/analgesic active ingredient identified, or any combination of anesthetic/analgesic active ingredients provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § 341.85.

(t) Any single oral nasal decongestant active ingredient identified in § 341.20(a) may be combined with any single antitussive active ingredient identified in § 341.14(a) or (b)(2) and any generally recognized as safe and effective single oral anesthetic/analgesic active ingredient, or any combination of anesthetic/analgesic active ingredients provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § 341.85. If the combination contains a topical antitussive, the product must be formulated in a solid dosage form to be dissolved in the mouth.

(u) Camphor identified in § 341.14(b)(1) may be combined with menthol identified in § 341.14(b)(2) and eucalyptus oil (1.2 to 1.3 percent) provided that the product is available only in a suitable ointment vehicle and provided that the product is labeled according to § 341.85.

(v) Levmetamfetamine identified in § 341.20(b)(1) may be combined with aromatics (camphor (54 milligrams (mg)), menthol (80 mg), methyl salicylate (11 mg), and lavender oil (4 mg)) provided that the product is available only as a nasal inhaler and provided that the product is labeled according to § 341.85.

(w) Any single antitussive active ingredient identified in § 341.14(a) or (b)(2) may be combined with any generally recognized as safe and effective single oral demulcent active ingredient provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § 341.85. If the combination contains a topical antitussive, the product must be formulated in a solid dosage form to be dissolved in the mouth.

(x) Any single oral nasal decongestant active ingredient identified in § 341.20(a) may be combined with any generally recognized as safe and effective single oral demulcent active ingredient provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § 341.85.

(y) Any single antitussive active ingredient identified in § 341.14(a) or (b)(2) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a) and any generally recognized as safe and effective single oral demulcent active ingredient provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § 341.85. If the combination contains a topical antitussive, the product must be formulated in a solid dosage form to be dissolved in the mouth.

(z) Any single antitussive active ingredient identified in § 341.14(a) or (b)(2) may be combined with any generally recognized as safe and effective single oral anesthetic/analgesic active ingredient or any combination of anesthetic/analgesic active ingredients and any generally recognized as safe and effective single oral demulcent active ingredient provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § 341.85. If the combination contains a topical antitussive, the product must be formulated in a solid dosage form to be dissolved in the mouth.

(aa) Any single oral nasal decongestant active ingredient identified in § 341.20(a) may be combined with any

generally recognized as safe and effective single oral anesthetic/analgesic active ingredient or any combination of oral anesthetic/analgesic active ingredients and any generally recognized as safe and effective single oral demulcent active ingredient provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § 341.85.

(bb) Any single antitussive active ingredient identified in § 341.14(a) or (b)(2) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a) and any generally recognized as safe and effective single oral anesthetic/analgesic active ingredient identified or any combination of anesthetic/analgesic active ingredients and any generally recognized as safe and effective single oral demulcent active ingredient provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § 341.85. If the combination contains a topical antitussive, the product must be formulated in a solid dosage form to be dissolved in the mouth.

[67 FR 78168, Dec. 23, 2002]

Subpart C—Labeling

§ 341.70 Labeling of OTC drug products containing ingredients that are used for treating concurrent symptoms (in either a single-ingredient or combination drug product).

The statements of identity, indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable.

(a) *For products containing diphenhydramine citrate and diphenhydramine hydrochloride identified in § 341.14(a)(5) and (a)(6).* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "antihistamine/cough suppressant" or "antihistamine/antitussive (cough suppressant)." The indications shall be combined from §§ 341.72(b) and 341.74(b). The warnings shall be combined from §§ 341.72(c)(1), (c)(2), (c)(4), and (c)(6) and 341.74(c)(1), (c)(2), (c)(3), and (c)(4). Alternatively, all of the warnings in § 341.74(c) shall be used. The directions for OTC labeling shall follow §§ 341.74(d)(1)(iv) or (d)(1)(v), as applicable. The directions for professional labeling shall follow § 341.90(j) or (k), as applicable.

(b) *For products containing menthol identified in §§ 341.14(b)(2) and 356.12(f) of this chapter.* The product contains 5 to 10 milligrams menthol. The labeling of the product contains the established name of the drug, if any, and identifies the product as a "cough suppressant/oral anesthetic" or "antitussive (cough suppressant)/oral anesthetic." The indications shall be combined from § 341.74(b) and part 356 of this chapter. The warnings shall be combined from § 341.74(c)(1), (c)(2), and (c)(3) and part 356 of this chapter. The directions shall be: "Directions [in bold type] [bullet][1] adults and children 2 years and over: dissolve lozenge slowly in the mouth. Repeat every 2 hours as needed or as directed by a doctor. [bullet] children under 2 years of age: ask a doctor".

[61 FR 15703, Apr. 9, 1996, as amended at 67 FR 78170, Dec. 23, 2002; 68 FR 17881, Apr. 14, 2003]

§ 341.72 Labeling of antihistamine drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "antihistamine."

(b) *Indications.* The labeling of the product states, under the heading "Indications," any of the phrases listed in paragraph (b) of this section, as appropriate. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce

[1] See § 201.66(b)(4) of this chapter for definition of bullet symbol.

of unapproved new drugs in violation of section 505(a) of the act.

(1) "Temporarily" (select one of the following: "relieves," "alleviates," "decreases," "reduces," or "dries") "runny nose and" (select one of the following: "relieves," "alleviates," "decreases," or "reduces") "sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever" (which may be followed by one or both of the following: "or other upper respiratory allergies" or "(allergic rhinitis)").

(2) "For the temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever" (which may be followed by one or both of the following: "or other upper respiratory allergies" or "(allergic rhinitis)").

(c) *Warnings.* The labeling of the product contains the following warnings, under the heading "Warnings":

(1) "May cause excitability especially in children."

(2) "Do not take this product, unless directed by a doctor, if you have a breathing problem such as emphysema or chronic bronchitis, or if you have glaucoma or difficulty in urination due to enlargement of the prostate gland."

(3) *For products containing brompheniramine maleate, chlorcyclizine hydrochloride, chlorpheniramine maleate, dexbrompheniramine maleate, dexchlorpheniramine maleate, phenindamine tartrate, pheniramine maleate, pyrilamine maleate, thonzylamine hydrochloride, or triprolidine hydrochloride identified in § 341.12(a), (b), (c), (d), (e), (i), (j), (k), (l), and (m).* "May cause drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery."

(4) *For products containing diphenhydramine citrate, diphenhydramine hydrochloride, or doxylamine succinate identified in § 341.12(f), (g), and (h).* "May cause marked drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery."

(5) *For products containing phenindamine tartrate identified in § 341.12(i).* "May cause nervousness and insomnia in some individuals."

(6) *For products that are labeled only for use by children under 12 years of age.* The labeling of the product contains only the warnings identified in paragraphs (c)(1) and (c)(5) of this section as well as the following:

(i) "Do not give this product to children who have a breathing problem such as chronic bronchitis, or who have glaucoma, without first consulting the child's doctor."

(ii) *For products containing brompheniramine maleate, chlorpheniramine maleate, dexbrompheniramine maleate, dexchlorpheniramine maleate, phenindamine tartrate, pheniramine maleate, pyrilamine maleate, thonzylamine hydrochloride, or triprolidine hydrochloride identified in § 341.12(a), (c), (d), (e), (i), (j), (k), (l), and (m).* "May cause drowsiness. Sedatives and tranquilizers may increase the drowsiness effect. Do not give this product to children who are taking sedatives or tranquilizers, without first consulting the child's doctor."

(iii) *For products containing diphenhydramine citrate, diphenhydramine hydrochloride, or doxylamine succinate identified in § 341.12(f), (g), and (h).* "May cause marked drowsiness. Sedatives and tranquilizers may increase the drowsiness effect. Do not give this product to children who are taking sedatives or tranquilizers, without first consulting the child's doctor."

(iv) *For products containing diphenhydramine citrate or diphenhydramine hydrochloride identified in § 341.12(f) and (g).* "Do not use [bullet][1] with any other product containing diphenhydramine, even one used on skin".

(7) *For products containing diphenhydramine citrate or*

[1] See § 201.66(b)(4) of this chapter for definition of bullet symbol.

diphenhydramine hydrochloride identified in § 341.12(f) and (g). "Do not use [bullet] with any other product containing diphenhydramine, even one used on skin".

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions":

(1) *For products containing brompheniramine maleate identified in § 341.12(a).* Adults and children 12 years of age and over: oral dosage is 4 milligrams every 4 to 6 hours, not to exceed 24 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(2) *For products containing chlorcyclizine hydrochloride identified in § 341.12(b).* Adults and children 12 years of age and over: oral dosage is 25 milligrams every 6 to 8 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children under 12 years of age: consult a doctor.

(3) *For products containing chlorpheniramine maleate identified in § 341.12(c).* Adults and children 12 years of age and over: oral dosage is 4 milligrams every 4 to 6 hours, not to exceed 24 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(4) *For products containing dexbrompheniramine maleate identified in § 341.12(d).* Adults and children 12 years of age and over: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(5) *For products containing dexchlorpheniramine maleate identified in § 341.12(e).* Adults and children 12 years of age and over: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(6) *For products containing diphenhydramine citrate identified in § 341.12(f).* Adults and children 12 years of age and over: oral dosage is 38 to 76 milligrams every 4 to 6 hours, not to exceed 456 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 19 to 38 milligrams every 4 to 6 hours, not to exceed 228 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(7) *For products containing diphenhydramine hydrochloride identified in § 341.12(g).* Adults and children 12 years of age and over: oral dosage is 25 to 50 milligrams every 4 to 6 hours, not to exceed 300 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 to 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(8) *For products containing doxylamine succinate identified in § 341.12(h).* Adults and children 12 years of age and over: oral dosage is 7.5 to 12.5 milligrams every 4 to 6 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 3.75 to 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(9) *For products containing phenindamine tartrate identified in § 341.12(i).* Adults and children 12 years of age and over: oral dosage is 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 milligrams every 4 to 6 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(10) *For products containing pheniramine maleate identified in § 341.12(j).* Adults and children 12 years of age and over: oral dosage is 12.5 to 25

milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 6.25 to 12.5 milligrams every 4 to 6 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(11) *For products containing pyrilamine maleate identified in § 341.12(k).* Adults and children 12 years of age and over: oral dosage is 25 to 50 milligrams every 6 to 8 hours, not to exceed 200 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 to 25 milligrams every 6 to 8 hours, not to exceed 100 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(12) *For products containing thonzylamine hydrochloride identified in § 341.12(l).* Adults and children 12 years of age and over: oral dosage is 50 to 100 milligrams every 4 to 6 hours, not to exceed 600 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 25 to 50 milligrams every 4 to 6 hours, not to exceed 300 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(13) *For products containing triprolidine hydrochloride identified in § 341.12(m).* Adults and children 12 years of age and over: oral dosage is 2.5 milligrams every 4 to 6 hours, not to exceed 10 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 1.25 milligrams every 4 to 6 hours, not to exceed 5 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this section.

[57 FR 58374, Dec. 9, 1992, as amended at 59 FR 4218, Jan. 28, 1994; 67 FR 72559, Dec. 6, 2002]

§ 341.74 Labeling of antitussive drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "cough suppressant" or an "antitussive (cough suppressant)."

(b) *Indications.* The labeling of the product states, under the heading "Indications," any of the phrases listed in this paragraph (b), as appropriate. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph, may also be used, as provided in § 330.1(c)(2), subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) "Temporarily" (select one of the following: "alleviates," "calms," "controls," "decreases," "quiets," "reduces," "relieves," or "suppresses") "cough due to" (select one of the following: "minor bronchial irritation" or "minor throat and bronchial irritation") (select one of the following: "as may occur with," "associated with," or "occurring with") (select one of the following: "A cold" or "the common cold") "or inhaled irritants."

(2) "Temporarily" (select one of the following: "alleviates," "calms," "controls," "decreases," "quiets," "reduces," "relieves," or "suppresses") "cough" (select one of the following: "as may occur with," "associated with," or "occurring with") (select one of the following: "A cold," "the common cold," or "inhaled irritants").

(3) In addition to the required information identified in paragraphs (b) (1) and (2) of this section, the labeling of the product may contain any (one or more) of the following statements:

(i) "Cough suppressant which temporarily" (select one of the following: "Alleviates," "controls," "decreases," "reduces," "relieves," or "suppresses") "the impulse to cough."

(ii) "Temporarily helps you cough less."

(iii) "Temporarily helps to" (select one of the following: "Alleviate," "control," "decrease," "reduce," "relieve," or "suppress") "the cough reflex that causes coughing."

(iv) "Temporarily" (select one of the following: "Alleviates," "controls," "decreases," "reduces," "relieves," or

"suppresses") "the intensity of coughing."

(v) (Select one of the following: "Alleviates," "Controls," "Decreases," "Reduces," "Relieves," or "Suppresses") (select one of the following: "Cough," "the impulse to cough," or "your cough") "to help you" (select one of the following: "Get to sleep," "sleep," or "rest").

(vi) *For products containing chlophedianol hydrochloride, codeine ingredients, dextromethorphan, or dextromethorphan hydrobromide identified in § 341.14(a) (1), (2), (3), and (4).* "Calms the cough control center and relieves coughing."

(vii) *For products containing chlophedianol hydrochloride, dextromethorphan, dextromethorphan hydrobromide, camphor, or menthol identified in § 341.14(a) (1), (3), (4) and (b) (1) and (2).* (*a*) "Nonnarcotic cough suppressant for the temporary" (select one of the following: "alleviation," "control," "decrease," "reduction," "relief," or "suppression") "of cough."

(*b*) (Select one of the following: "Alleviates," "Controls," "Decreases," "Reduces," "Relieves," or "Suppresses") "cough impulses without narcotics."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For oral and topical antitussives.* "A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur, or is accompanied by fever, rash, or persistent headache, consult a doctor."

(2) *For oral and topical antitussives labeled for adults or for adults and children under 12 years of age.* "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor."

(3) *For oral and topical antitussives labeled only for children under 12 years of age.* "Do not give this product for persistent or chronic cough such as occurs with asthma or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor."

(4) *Oral antitussives*—(i) *For products containing codeine ingredients identified in § 341.14(a)(2).* "May cause or aggravate constipation."

(ii) *For products containing codeine ingredients identified in § 341.14(a)(2) when labeled only for adults.* "Do not take this product if you have a chronic pulmonary disease or shortness of breath unless directed by a doctor."

(iii) *For products containing codeine ingredients identified in § 341.14(a)(2) when labeled only for children under 12 years of age.* "Do not give this product to children who have a chronic pulmonary disease, shortness of breath, or who are taking other drugs unless directed by a doctor."

(iv) *For products containing codeine ingredients identified in § 341.14(a)(2) when labeled for use in adults and children under 12 years of age.* "Adults and children who have a chronic pulmonary disease or shortness of breath, or children who are taking other drugs, should not take this product unless directed by a doctor."

(v) *For products containing dextromethorphan or dextromethorphan hydrobromide as identified in § 341.14 (a)(3) and (a)(4) when labeled for adults or for adults and children under 12 years of age. Drug interaction precaution.* "Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product."

(vi) *For products containing dextromethorphan or dextromethorphan hydrobromide as identified in § 341.14 (a)(3) and (a)(4) when labeled only for children under 12 years of age. Drug interaction precaution.* "Do not use in a child who is taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your child's prescription drug contains an MAOI, ask a doctor or pharmacist before giving this product."

(vii) *For products containing diphenhydramine citrate or diphenhydramine hydrochloride identified*

in § 341.14 (a)(5) and (a)(6). "May cause excitability especially in children."

(viii) *For products containing diphenhydramine citrate or diphenhydramine hydrochloride identified in § 341.14 (a)(5) and (a)(6) when labeled only for children under 12 years of age*—(A) "Do not give this product to children who have a breathing problem such as chronic bronchitis, or who have glaucoma, without first consulting the child's doctor."

(B) "May cause marked drowsiness. Sedatives and tranquilizers may increase the drowsiness effect. Do not give this product to children who are taking sedatives or tranquilizers, without first consulting the child's doctor."

(C) "Do not use [bullet][1] with any other product containing diphenhydramine, even one used on skin".

(ix) *For products containing diphenhydramine citrate or diphenhydramine hydrochloride identified in § 341.14 (a)(5) and (a)(6) when labeled for use in adults and children under 12 years of age*—(A) "Do not take this product, unless directed by a doctor, if you have a breathing problem such as emphysema or chronic bronchitis, or if you have glaucoma or difficulty in urination due to enlargement of the prostate gland."

(B) "May cause marked drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery."

(C) "Do not use [bullet] with any other product containing diphenhydramine, even one used on skin".

(5) *Topical antitussives*—(i) *For products containing camphor or menthol identified in § 341.14 (b) (1) and (2) in a suitable ointment vehicle.* "For external use only. Do not take by mouth or place in nostrils."

(ii) *For products containing camphor or menthol identified in § 341.14(b) (1) and (2) for steam inhalation use.* "For steam inhalation only. Do not take by mouth."

(iii) *For any product containing camphor or menthol in a suitable ointment vehicle or for steam inhalation use and meets the definition of one of the signal words ("extremely flammable," "flammable," "combustible") as described in 16 CFR 1500.3(b)(10).* The labeling contains the appropriate flammability signal word(s) followed by a colon and the statement "Keep away from fire or flame."

(iv) *For any product containing camphor or menthol in a suitable ointment vehicle and that does not contain a flammability signal word as described in 16 CFR 1500.3(b)(10).* "When using this product, do not [bullet][1] heat [bullet] microwave [bullet] add to hot water or any container where heating water. May cause splattering and result in burns." [Information highlighted in bold type.]

(v) *For any product containing camphor or menthol in a suitable ointment vehicle and that contains a flammability signal word as described in 16 CFR 1500.3(b)(10).* "When using this product, do not [bullet] heat [bullet] microwave [bullet] use near an open flame [bullet] add to hot water or any container where heating water. May cause splattering and result in burns." [Information highlighted in bold type.]

(vi) *For any product containing camphor or menthol for steam inhalation use.* "When using this product, do not [bullet] heat [bullet] microwave [bullet] use near an open flame [bullet] add to hot water or any container where heating water except when adding to cold water only in a hot steam vaporizer. May cause splattering and result in burns." [Information highlighted in bold type.]

(vii) *For any product formulated in a volatile vehicle.* The labeling contains the following statement under the heading "Other information": "Close container tightly and store at room temperature away from heat."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions":

[1] See § 201.66(b)(4) of this chapter for definition of bullet symbol.

[1] For a definition of the term "bullet," see § 201.66(b)(4) of this chapter.

(1) *Oral antitussives*—(i) *For products containing chlophedianol hydrochloride identified in § 341.14(a)(1).* Adults and children 12 years of age and over: Oral dosage is 25 milligrams every 6 to 8 hours, not to exceed 100 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: Oral dosage is 12.5 milligrams every 6 to 8 hours, not to exceed 50 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: Consult a doctor.

(ii) *For products containing codeine ingredients identified in § 341.14(a)(2).* Adults and children 12 years of age and over: Oral dosage is 10 to 20 milligrams every 4 to 6 hours, not to exceed 120 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: Oral dosage is 5 to 10 milligrams every 4 to 6 hours, not to exceed 60 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: Consult a doctor. A special measuring device should be used to give an accurate dose of this product to children under 6 years of age. Giving a higher dose than recommended by a doctor could result in serious side effects for your child.

(iii) *For products containing dextromethorphan or dextromethorphan hydrobromide identified in § 341.14(a) (3) and (4).* The dosage is equivalent to dextromethorphan hydrobromide. Adults and children 12 years of age and over: Oral dosage is 10 to 20 milligrams every 4 hours or 30 milligrams every 6 to 8 hours, not to exceed 120 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: Oral dosage is 5 to 10 milligrams every 4 hours or 15 milligrams every 6 to 8 hours, not to exceed 60 milligrams in 24 hours, or as directed by a doctor. Children 2 to under 6 years of age: Oral dosage is 2.5 to 5 milligrams every 4 hours or 7.5 milligrams every 6 to 8 hours, not to exceed 30 milligrams in 24 hours, or as directed by a doctor. Children under 2 years of age: Consult a doctor.

(iv) *For products containing diphenhydramine citrate identified in § 341.14(a)(5).* Adults and children 12 years of age and over: oral dosage is 38 milligrams every 4 hours, not to exceed 228 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 19 milligrams every 4 hours, not to exceed 114 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(v) *For products containing diphenhydramine hydrochloride identified in § 341.14(a)(6).* Adults and children 12 years of age and over: oral dosage is 25 milligrams every 4 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 milligrams every 4 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(2) *Topical antitussives*—(i) *For products containing camphor identified in § 341.14(b)(1) in a suitable ointment vehicle.* The product contains 4.7 to 5.3 percent camphor. "[bullet] see important warnings under 'When using this product' [appears as the first statement under the heading "Directions" and is highlighted in bold type] [bullet] adults and children 2 years and older: [bullet] rub on the throat and chest in a thick layer [bullet] cover with a warm, dry cloth if desired [bullet] clothing should be loose about throat and chest to help vapors reach the nose and mouth [bullet] use up to three times daily or as directed by a doctor [bullet] children under 2 years of age: Ask a doctor.

(ii) *For products containing menthol identified in § 341.14(b)(2) in a suitable ointment vehicle.* The product contains 2.6 to 2.8 percent menthol. "[bullet] see important warnings under 'When using this product' " [appears as the first statement under the heading "Directions" and is highlighted in bold type] [bullet] adults and children 2 years and older: [bullet] rub on the throat and chest in a thick layer [bullet] cover with a warm, dry cloth if desired [bullet] clothing should be loose about throat and chest to help vapors reach the nose and mouth [bullet] use up to three times daily or as directed by a doctor [bullet] children under 2 years of age: Ask a doctor.

(iii) *For products containing menthol identified in § 341.14(b)(2) in a lozenge.* The product contains 5 to 10 milligrams menthol. Adults and children 2 to under 12 years of age: Allow lozenge

to dissolve slowly in the mouth. May be repeated every hour as needed or as directed by a doctor. Children under 2 years of age: Consult a doctor.

(iv) *For products containing camphor identified in § 341.14(b)(1) for steam inhalation use.* The product contains 6.2 percent camphor. "[bullet] see important warnings under 'When using this product' " [appears as the first statement under the heading "Directions" and is highlighted in bold type] [bullet] adults and children 2 years and older: (select one of the following, as appropriate: *For products formulated to be added directly to cold water inside a hot steam vaporizer.* [bullet] use 1 tablespoonful of solution for each quart of water or 1½ teaspoonsful of solution for each pint of water [bullet] add solution directly to cold water only in a hot steam vaporizer [bullet] follow manufacturer's directions for using vaporizer or *For products formulated to be placed in the medication chamber of a hot steam vaporizer.* [bullet] place water in the vaporizer and follow manufacturer's directions for using vaporizer [bullet] place solution in the medication chamber only) [bullet] breathe in the medicated vapors [bullet] use up to three times daily or as directed by a doctor [bullet] children under 2 years of age: Ask a doctor.

(v) *For products containing menthol identified in § 341.14(b)(2) for steam inhalation use.* The product contains 3.2 percent menthol. "[bullet] see important warnings under 'When using this product' "[appears as the first statement under the heading "Directions" and is highlighted in bold type] [bullet] adults and children 2 years and older: (select one of the following, as appropriate: *For products formulated to be added directly to cold water inside a hot steam vaporizer.* [bullet] use 1 tablespoonful of solution for each quart of water or 1½ teaspoonsful of solution for each pint of water [bullet] add solution directly to cold water only in a hot steam vaporizer [bullet] follow manufacturer's directions for using vaporizer or *For products formulated to be placed in the medication chamber of a hot steam vaporizer.* [bullet] place water in the vaporizer and follow manufacturer's directions for using vaporizer [bullet] place solution in the medication chamber only) [bullet] breathe in the medicated vapors [bullet] use up to three times daily or as directed by a doctor [bullet] children under 2 years of age: Ask a doctor.

(e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this section.

(f) *Exemption from the general accidental overdose warning.* The labeling for antitussive drug products containing the active ingredient identified in § 341.14(b)(2) marketed in accordance with § 341.74(d)(2)(iii) is exempt from the requirement in § 330.1(g) of this chapter that the labeling bear the general warning statement "In case of accidental overdose, seek professional assistance or contact a poison control center immediately." The labeling must continue to bear the first part of the general warning in § 330.1(g) of this chapter, which states, "Keep this and all drugs out of the reach of children."

[52 FR 30055, Aug. 12, 1987; 52 FR 35610, Sept. 22, 1987; 53 FR 35809, Sept. 15, 1988; 55 FR 27808, July 6, 1990; 55 FR 40383, Oct. 3, 1990; 58 FR 54236, Oct. 20, 1993; 59 FR 29174, June 3, 1994; 59 FR 36051, July 15, 1994; 64 FR 13295, Mar. 17, 1999; 65 FR 8, Jan. 3, 2000; 65 FR 46867, Aug. 1, 2000; 67 FR 72559, Dec. 6, 2002]

§ 341.76 Labeling of bronchodilator drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "bronchodilator."

(b) *Indications.* The labeling of the product states, under the heading "Indications," the phrase listed in paragraph (b)(1) of this section. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph (b), may also be used, as provided in § 330.1(c)(2), subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) "For temporary relief of shortness of breath, tightness of chest, and wheezing due to bronchial asthma."

(2) In addition to the required information identified in paragraph (b)(1) of this section, the labeling of the product may contain one or more of the following statements:

(i) "For the" (select one of the following: "temporary relief" or "symptomatic control") "of bronchial asthma."

(ii) "Eases breathing for asthma patients" (which may be followed by: "by reducing spasms of bronchial muscles").

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) "Do not use this product unless a diagnosis of asthma has been made by a doctor."

(2) "Do not use this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

(3) "Do not use this product if you have ever been hospitalized for asthma or if you are taking any prescription drug for asthma unless directed by a doctor."

(4) *Drug interaction precaution.* "Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product."

(5) *For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, or racephedrine hydrochloride identified in § 341.16 (a), (b), (c), and (f).* (i) "Do not continue to use this product, but seek medical assistance immediately if symptoms are not relieved within 1 hour or become worse."

(ii) "Some users of this product may experience nervousness, tremor, sleeplessness, nausea, and loss of appetite. If these symptoms persist or become worse, consult your doctor."

(6) *For products containing epinephrine, epinephrine bitartrate, or racepinephrine hydrochloride identified in § 341.16 (d), (e), and (g).* (i) "Do not use this product more frequently or at higher doses than recommended unless directed by a doctor. [first sentence in boldface type] Excessive use may cause nervousness and rapid heart beat, and, possibly, adverse effects on the heart."

(ii) "Do not continue to use this product, but seek medical assistance immediately if symptoms are not relieved within 20 minutes or become worse." [sentence in boldface type]

(iii) *For products intended for use in a hand-held rubber bulb nebulizer.* "Do not use this product if it is brown in color or cloudy."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions":

(1) *For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, or racephedrine hydrochloride identified in § 341.16 (a), (b), (c), and (f).* Adults and children 12 years of age and over: Oral dosage is 12.5 to 25 milligrams every 4 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Do not exceed recommended dose unless directed by a doctor. Children under 12 years of age: Consult a doctor.

(2) *For products containing epinephrine, epinephrine bitartrate, and racepinephrine hydrochloride identified in § 341.16(d), (e), and (g) for use in a hand-held rubber bulb nebulizer.* The ingredient is used in an aqueous solution at a concentration equivalent to 1 percent epinephrine. Inhalation dosage for adults, children 12 years of age and over, and children 4 to under 12 years of age: 1 to 3 inhalations not more often than every 3 hours. The use of this product by children should be supervised by an adult. Children under 4 years of age: Consult a doctor.

(Collection of information requirement approved by the Office of Management and Budget under control number 0910–0237)

[51 FR 35339, Oct. 2, 1986, as amended at 52 FR 7126, Mar. 9, 1987; 52 FR 7830, Mar. 13, 1987; 53 FR 35810, Sept. 15, 1988; 58 FR 54242, Oct. 20, 1993; 61 FR 25146, May 20, 1996; 62 FR 9684, Mar. 4, 1997; 64 FR 13295, Mar. 17, 1999]

§ 341.78 Labeling of expectorant drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "expectorant."

(b) *Indications.* The labeling of the product states, under the heading "Indications," the following: "Helps loosen phlegm (mucus) and thin bronchial secretions to" (select one or more of the following: "rid the bronchial passageways of bothersome mucus," "drain bronchial tubes," and "make coughs more productive"). Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph (b), may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(c) *Warnings.* The labeling of the product contains the following warnings, under the heading "Warnings":

(1) "A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur, or is accompanied by a fever, rash, or persistent headache, consult a doctor."

(2) *For expectorant drug products labeled for adults or for adults and children under 12 years of age.* "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, chronic bronchitis, or emphysema, or where cough is accompanied by excessive phlegm (mucus) unless directed by a doctor."

(3) *For expectorant drug products labeled only for children under 12 years of age.* "Do not give this product for persistent or chronic cough such as occurs with asthma or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions" for products containing guaifenesin identified in § 341.18: Adults and children 12 years of age and over: oral dosage is 200 to 400 milligrams every 4 hours not to exceed 2,400 milligrams in 24 hours. Children 6 to under 12 years of age: oral dosage is 100 to 200 milligrams every 4 hours not to exceed 1,200 milligrams in 24 hours. Children 2 to under 6 years of age: oral dosage is 50 to 100 milligrams every 4 hours not to exceed 600 milligrams in 24 hours. Children under 2 years of age: consult a doctor.

(e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this section.

[54 FR 8509, Feb. 28, 1989, as amended at 57 FR 29177, June 30, 1992]

§ 341.80 Labeling of nasal decongestant drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "nasal decongestant."

(b) *Indications.* The labeling of the product states, under the heading "Indications," the phrase listed in paragraph (b)(1) of this section, as appropriate, and may contain any additional phrases listed in paragraph (b)(2) of this section. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in paragraphs (b)(1) and (b)(2) of this section, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) (Select one of the following: "For the temporary relief of nasal congestion" or "Temporarily relieves nasal congestion") (which may be followed by any of the following in paragraphs (b)(1) (i), (ii), and (iii) of this section):

(i) "due to" (select one of the following: "the common cold" or "a cold").

(ii) "due to" (select one of the following: "hay fever," "hay fever (allergic rhinitis)," "hay fever or other upper respiratory allergies," or "hay fever or other upper respiratory allergies (allergic rhinitis)").

(iii) "associated with sinusitis."

(2) In addition to the information identified in paragraph (b)(1) of this section, the labeling of the product may contain any (one or more) of the following statements:

(i) (Select one of the following: "For the temporary relief of" or "Temporarily relieves") (select one of the following: "stuffy nose," "stopped up nose," "nasal stuffiness," or "clogged up nose.")

(ii) (Select one of the following: "Reduces swelling of," "Decongests," or "Helps clear") "nasal passages; shrinks swollen membranes."

(iii) "Temporarily restores freer breathing through the nose."

(iv) "Helps decongest sinus openings and passages; temporarily relieves sinus congestion and pressure."

(v) "Promotes nasal and/or sinus drainage; temporarily relieves sinus congestion and pressure."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *Oral nasal decongestants*—(i) *For products containing phenylephrine hydrochloride, pseudoephedrine hydrochloride, pseudoephedrine sulfate, or phenylephrine bitartrate identified in § 341.20 (a)(1) through (a)(4) when labeled for adults.* (A) "Do not exceed recommended dosage. [first sentence in boldface type] If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a doctor."

(B) "If symptoms do not improve within 7 days or are accompanied by fever, consult a doctor."

(C) "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

(D) *Drug interaction precaution.* "Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product."

(ii) *For products containing phenylephrine hydrochloride, pseudoephedrine hydrochloride, pseudoephedrine sulfate, or phenylephrine bitartrate identified in § 341.20 (a)(1) through (a)(4) when labeled for children under 12 years of age.* (A) "Do not exceed recommended dosage. [first sentence in boldface type] If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a doctor."

(B) "If symptoms do not improve within 7 days or are accompanied by fever, consult a doctor."

(C) "Do not give this product to a child who has heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor."

(D) *Drug interaction precaution.* "Do not use in a child who is taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your child's prescription drug contains an MAOI, ask a doctor or pharmacist before giving this product."

(iii) *For oral nasal decongestant products labeled for both adults and children under 12 years of age.* The labeling of the product contains the warnings identified in paragraph (c)(1)(i) of this section.

(2) *Topical nasal decongestants*—(i) *For products containing any topical nasal decongestant identified in § 341.20(b) when labeled for adults.* (A) "Do not exceed recommended dosage." [sentence in boldface type]

(B) "This product may cause temporary discomfort such as burning, stinging, sneezing, or an increase in nasal discharge."

(C) "The use of this container by more than one person may spread infection."

(ii) *For products containing levmetamfetamine identified in § 341.20(b)(1) when used in an inhalant dosage form and when labeled for adults.* "Do not use this product for more than 7 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, ask a doctor."

(iii) *For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, or xylometazoline hydrochloride identified in § 341.20 (b)(2), (b)(3), (b)(4), (b)(6), (b)(7), (b)(8), and (b)(10) when used as nasal sprays, drops, or jellies and when labeled for adults.* (A) "Do not use this product for more than 3 days. Use only as directed. Frequent

or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor."

(B) "Do not use this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

(iv) *For products containing naphazoline hydrochloride identified in § 341.20(b)(6) at a concentration of 0.05 percent.* "Do not use this product in children under 12 years of age because it may cause sedation if swallowed."

(v) *For products containing propylhexedrine identified in § 341.20(b)(9) when used in an inhalant dosage form and when labeled for adults.* "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor."

(vi) *For products containing any topical nasal decongestant identified in § 341.20(b) when labeled for children under 12 years of age.* The labeling of the product contains the warnings identified in paragraph (c)(2)(i) of this section.

(vii) *For products containing levmetamfetamine identified in § 341.20(b)(1) when used in an inhalant dosage form and when labeled for children under 12 years of age.* "Do not use this product for more than 7 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, ask a doctor."

(viii) *For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, or xylometazoline hydrochloride identified in § 341.20(b)(2), (b)(3), (b)(4), (b)(6), (b)(7), (b)(8), and (b)(10) when used as nasal sprays, drops, or jellies and when labeled for children under 12 years of age.* (A) "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor."

(B) "Do not use this product in a child who has heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor."

(ix) *For products containing propylhexedrine identified in § 341.20(b)(9) when used in an inhalant dosage form and when labeled for children under 12 years of age.* "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor."

(x) *For topical nasal decongestant products labeled for both adults and for children under 12 years of age.* The labeling of the product contains the applicable warnings identified in paragraphs (c)(2)(i), (c)(2)(ii), (c)(2)(iii), and (c)(2)(v) of this section.

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions":

(1) *Oral nasal decongestants*—(i) *For products containing phenylephrine hydrochloride identified in § 341.20(a)(1).* Adults and children 12 years of age and over: 10 milligrams every 4 hours not to exceed 60 milligrams in 24 hours. Children 6 to under 12 years of age: 5 milligrams every 4 hours not to exceed 30 milligrams in 24 hours. Children 2 to under 6 years of age: 2.5 milligrams every 4 hours not to exceed 15 milligrams in 24 hours. Children under 2 years of age: consult a doctor.

(ii) *For products containing pseudoephedrine hydrochloride or pseudoephedrine sulfate identified in § 341.20 (a)(2) and (a)(3).* Adults and children 12 years of age and over: 60 milligrams every 4 to 6 hours not to exceed 240 milligrams in 24 hours. Children 6 to under 12 years of age: 30 milligrams every 4 to 6 hours not to exceed 120 milligrams in 24 hours. Children 2 to under 6 years of age: 15 milligrams every 4 to 6 hours not to exceed 60 milligrams in 24 hours. Children under 2 years of age: consult a doctor.

(iii) *For products containing phenylephrine bitartrate identified in § 341.20(a)(4).* Include information on the number of dosage units and the quantity of water the dosage units are to be dissolved in prior to administration as shown in the following table:

Age[1]	Dose[1]
Adults and children 12 years of age and over	15.6 milligrams every 4 hours not to exceed 62.4 milligrams in 24 hours
Children 6 to under 12 years of age	7.8 milligrams every 4 hours not to exceed 31.2 milligrams in 24 hours
Children under 6 years of age	Ask a doctor

[1]Headings are not required to appear in the product's labeling

(2) *Topical nasal decongestants*—(i) *For products containing levmetamfetamine identified in § 341.20(b)(1) when used in an inhalant dosage form.* The product delivers in each 800 milliliters of air 0.04 to 0.150 milligrams of levmetamfetamine. Adults: 2 inhalations in each nostril not more often than every 2 hours. Children 6 to under 12 years of age (with adult supervision): 1 inhalation in each nostril not more often than every 2 hours. Children under 6 years of age: ask a doctor.

(ii) *For products containing ephedrine, ephedrine hydrochloride, or ephedrine sulfate identified in § 341.20(b) (2), (3), and (4)*—(A) *Nasal drops or sprays—For a 0.5-percent aqueous solution.* Adults and children 12 years of age and over: 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Children 6 to under 12 years of age (with adult supervision): 1 or 2 drops or sprays in each nostril not more often than every 4 hours. Children under 6 years of age: consult a doctor.

(B) *Nasal jelly—For a 0.5-percent water-based jelly.* Adults and children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 4 hours.

(iii) *For products containing naphazoline hydrochloride identified in § 341.20(b)(6)*—(A) *Nasal drops or sprays—(1) For a 0.05-percent aqueous solution.* Adults and children 12 years of age and over: 1 or 2 drops or sprays in each nostril not more often than every 6 hours. Do not give to children under 12 years of age unless directed by a doctor.

(2) *For a 0.025-percent aqueous solution.* Children 6 to under 12 years of age (with adult supervision): 1 or 2 drops or sprays in each nostril not more often than every 6 hours. Children under 6 years of age: consult a doctor.

(B) *Nasal jelly—(1) For a 0.05-percent water-based jelly.* Adults and children 12 years of age and over: place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 6 hours. Do not give to children under 12 years of age unless directed by a doctor.

(2) *For a 0.025-percent water-based jelly.* Children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 6 hours. Children under 6 years of age: consult a doctor.

(iv) *For products containing oxymetazoline hydrochloride identified in § 341.20(b)(7)*—(A) *Nasal drops or sprays—(1) For a 0.05-percent aqueous solution.* Adults and children 6 to under 12 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 10 to 12 hours. Do not exceed 2 doses in any 24-hour period. Children under 6 years of age: consult a doctor.

(2) *A 0.025-percent aqueous solution in a container having either a calibrated dropper or a metered-dose spray that delivers no more than 0.027 milligrams of oxymetazoline per three drops or three sprays.* Children 2 to under 6 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 10 to 12 hours. Use only recommended amount. Do not exceed 2 doses in any 24-hour period. [previous two sentences in boldface type] Children under 2 years of age: consult a doctor.

(B) *Nasal jelly—For a 0.05-percent water-based jelly.* Adults and children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 10 to 12 hours. Do not exceed 2 doses in any 24-hour period. Children under 6 years of age: consult a doctor.

(v) *For products containing phenylephrine hydrochloride identified in § 341.20(b)(8)*—(A) *Nasal drops or sprays—(1) For a 1-percent aqueous solution.* Adults and children 12 years of age and

over: 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Do not give to children under 12 years of age unless directed by a doctor.

(*2*) *For a 0.5-percent aqueous solution.* Adults and children 12 years of age and over: 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Do not give to children under 12 years of age unless directed by a doctor.

(*3*) *For a 0.25-percent aqueous solution.* Adults and children 6 to under 12 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Children under 6 years of age: consult a doctor.

(*4*) *A 0.125-percent aqueous solution in a container having either a calibrated dropper or a metered-dose spray that delivers no more than 0.135 milligrams of phenylephrine per three drops or three sprays.* Children 2 to under 6 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Use only recommended amount. [previous sentence in boldface type] Children under 2 years of age: consult a doctor.

(B) *Nasal jelly—(1) For a 1-percent water-based jelly.* Adults and children 12 years of age and over: place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 4 hours. Do not give to children under 12 years of age unless directed by a doctor.

(*2*) *For a 0.5-percent water-based jelly.* Adults and children 12 years of age and over: place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 4 hours. Do not give to children under 12 years of age unless directed by a doctor.

(*3*) *For a 0.25-percent water-based jelly.* Adults and children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 4 hours. Children under 6 years of age: consult a doctor.

(vi) *For products containing propylhexedrine identified in § 341.20(b)(9) when used in an inhalant dosage form.* The product delivers in each 800 milliliters of air 0.40 to 0.50 milligrams of propylhexedrine. Adults and children 6 to under 12 years of age (with adult supervision): 2 inhalations in each nostril not more often than every 2 hours. Children under 6 years of age: consult a doctor.

(vii) *For products containing xylometazoline hydrochloride identified in § 341.20(b)(10)*—(A) *Nasal drops or sprays—(1) For a 0.1-percent aqueous solution.* Adults and children 12 years of age and over: 2 or 3 drops or sprays in each nostril not more often than every 8 to 10 hours. Do not give to children under 12 years of age unless directed by a doctor.

(*2*) *A 0.05-percent aqueous solution in a container having either a calibrated dropper or a metered-dose spray that delivers no more than 0.054 milligrams of xylometazoline per three drops or three sprays.* Children 6 to under 12 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 8 to 10 hours. Children 2 to under 6 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 8 to 10 hours. Use only recommended amount. Do not exceed 3 doses in any 24-hour period. [previous two sentences in boldface type] Children under 2 years of age: consult a doctor.

(B) *Nasal jelly—(1) For a 0.1-percent water-based jelly.* Adults and children 12 years of age and over: place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 8 to 10 hours. Do not give to children under 12 years of age unless directed by a doctor.

(*2*) *For a 0.05-percent water-based jelly.* Children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 8 to 10 hours. Children under 6 years of age: consult a doctor.

(viii) *Other required statements—For products containing levmetamfetamine or propylhexedrine identified in § 341.20(b)(1) or (b)(9) when used in an inhalant dosage form.* (A) "This inhaler is effective for a minimum of 3 months after first use."

(B) "Keep inhaler tightly closed."

[59 FR 43409, Aug. 23, 1994, as amended at 63 FR 40650, July 30, 1998; 64 FR 13295, Mar. 17, 1999; 65 FR 8, Jan. 3, 2000; 71 FR 43362, Aug. 1, 2006]

EFFECTIVE DATE NOTE: At 70 FR 58977, Oct. 11, 2005, § 341.80 was amended by removing paragraph (b)(1)(iii), effective Apr. 11, 2007.

§ 341.85 Labeling of permitted combinations of active ingredients.

The statements of identity, indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable.

(a) *Statement of identity.* For a combination drug product that has an established name, the labeling of the product states the established name of the combination drug product, followed by the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC drug monographs. If there is no established name, the labeling of the product states the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph (a).

(1) *For permitted combinations identified in § 341.40(a), (c), (f), (g), (l), (m), (n), (o), (q), and (r) containing an analgesic-antipyretic active ingredient.* The analgesic-antipyretic component of the product shall be identified as a "pain reliever" or "analgesic (pain reliever)." If the product is also labeled to relieve fever, then the analgesic-antipyretic component is identified as a "pain reliever-fever reducer" or "analgesic (pain reliever)-antipyretic (fever reducer)."

(2) [Reserved]

(b) *Indications.* The labeling of the product states, under the heading "Uses," the indication(s) for each ingredient in the combination, as established in the indications sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph (b). Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in the applicable OTC drug monographs or listed in this paragraph (b), may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) *For permitted combinations containing an analgesic-antipyretic active ingredient identified in § 341.40(a), (c), (f), (g), (l), (m), (n), (o), (q), and (r) when labeled for relief of general cough-cold symptoms and/or the common cold.* (i) The labeling for the analgesic-antipyretic ingredients states "[bullet] temporarily relieves [bullet] minor aches and pains [bullet] headache" and "[bullet] temporarily reduces fever".

(ii) The labeling for the cough-cold ingredient(s) may follow a separate bullet(s) or may be combined with the relieves part of the indication in paragraph (b)(1)(i) of this section.

(2) *For permitted combinations containing an analgesic-antipyretic active ingredient identified in § 341.40 (a), (c), (f), (g), (m), (q), and (r) when labeled for relief of hay fever/allergic rhinitis and/or nasal congestion symptoms.* (i) The labeling for the analgesic-antipyretic ingredients states "[bullet] temporarily relieves [bullet] minor aches and pains [bullet] headache".

(ii) The indication(s) for the cough-cold ingredient(s) consists of the labeling for antihistamines in § 341.72(b)(1) or (b)(2) and/or nasal decongestants in § 341.80(b)(1)(ii) and/or (b)(1)(iii), as appropriate, and the labeling for any other cough-cold ingredient present in the combination. This labeling may follow a separate bullet(s) or may be combined with the indication in paragraph (b)(2)(i) of this section.

(3) *For permitted combinations containing an oral analgesic-antipyretic active ingredient identified in § 341.40 (a), (c), (f), (g), (m), (q), and (r) when labeled for relief of general cough-cold symptoms and/or the common cold and for relief of hay fever/allergic rhinitis and/or nasal congestion symptoms.* The labeling states both indications in paragraphs (b)(1) and (b)(2) of this section.

(4) *For permitted combinations containing an oral anesthetic-analgesic active ingredient identified in § 341.40(k), (s), (t), (z), (aa), and (bb).* The labeling for the anesthetic-analgesic ingredients in part 356 of this chapter should be used.

(5) *For permitted combinations containing camphor, menthol, and eucalyptus oil identified in § 341.40(u).* The labeling for antitussive ingredients in § 341.74(b) should be used.

(6) *For permitted combinations containing levmetamfetamine with aromatics identified in § 341.40(v).* The labeling for nasal decongestant ingredients in § 341.80(b) should be used.

(7) *Other allowable statements.* In addition to the required information identified in paragraph (b) of this section, the labeling of the combination drug product may contain any of the "other allowable statements" (if any), that are identified in the applicable OTC drug monographs, provided such statements are neither placed in direct conjunction with information required to appear in the labeling nor occupy labeling space with greater prominence or conspicuousness than the required information.

(c) *Warnings.* The labeling of the product states, under the heading "Warnings," the warning(s) for each ingredient in the combination, as established in the warnings sections of the applicable OTC drug monographs, unless otherwise stated in paragraph (c) of this section.

(1) *For permitted combinations containing an antitussive and an analgesic-antipyretic identified in § 341.40(f), (g), (l), and (m).* The labeling states the following warnings:

(i) *For products labeled only for adults.* The following warning should be used instead of the warnings in § 341.74(c)(1) and part 343 of this chapter: "Stop use and ask a doctor if [in bold type] [bullet] pain or cough gets worse or lasts more than 7 days [bullet] fever gets worse or lasts more than 3 days [bullet] redness or swelling is present [bullet] new symptoms occur [bullet] cough comes back or occurs with rash or headache that lasts. These could be signs of a serious condition."

(ii) *For products labeled only for children under 12 years of age.* The following warning should be used instead of the warnings in § 341.74(c)(3) and part 343 of this chapter: "Stop use and ask a doctor if [in bold type] [bullet] pain or cough gets worse or lasts more than 5 days [bullet] fever gets worse or lasts more than 3 days [bullet] redness or swelling is present [bullet] new symptoms occur [bullet] cough comes back or occurs with rash or headache that lasts. These could be signs of a serious condition."

(iii) *For products labeled for both adults and for children under 12 years of age.* The following warning should be used instead of the warnings in § 341.74(c)(2) and part 343 of this chapter: "Stop use and ask a doctor if [in bold type] [bullet] pain or cough gets worse or lasts more than 5 days (children) or 7 days (adults) [bullet] fever gets worse or lasts more than 3 days [bullet] redness or swelling is present [bullet] new symptoms occur [bullet] cough comes back or occurs with rash or headache that lasts. These could be signs of a serious condition."

(2) *For permitted combinations containing an expectorant and an analgesic-antipyretic identified in § 341.40(o).* The labeling states the following warnings:

(i) *For products labeled only for adults.* The warning in paragraph (c)(1)(i) of this section should be used instead of the warnings in § 341.78(c)(3) and part 343 of this chapter.

(ii) *For products labeled only for children under 12 years of age.* The warning in paragraph (c)(1)(ii) of this section should be used instead of the warnings in § 341.78(c)(3) and part 343 of this chapter.

(iii) *For products labeled for both adults and for children under 12 years of age.* The warning in paragraph (c)(1)(iii) of this section should be used instead of the warnings in § 341.78(c)(3) and part 343 of this chapter.

(3) *For permitted combinations containing a nasal decongestant and an analgesic-antipyretic identified in § 341.40(c), (g), (m), (n), (q), and (r).* The labeling states the following warnings:

(i) *For products labeled only for adults.* The following warning should be used instead of the warnings in § 341.80(c)(1)(i)(B) and part 343 of this chapter: "Stop use and ask a doctor if [in bold type] [bullet] pain or nasal congestion gets worse or lasts more

than 7 days [bullet] fever gets worse or lasts more than 3 days [bullet] redness or swelling is present [bullet] new symptoms occur".

(ii) *For products labeled for only children under 12 years of age.* The following warning should be used instead of the warnings in § 341.80(c)(1)(ii)(B) and part 343 of this chapter: "Stop use and ask a doctor if [in bold type] [bullet] pain or nasal congestion gets worse or lasts more than 5 days [bullet] fever gets worse or lasts more than 3 days [bullet] redness or swelling is present [bullet] new symptoms occur".

(iii) *For products labeled for both adults and children under 12 years of age.* The following warning should be used instead of the warnings in § 341.80(c)(1)(iii) and part 343 of this chapter: "Stop use and ask a doctor if [in bold type] [bullet] pain or nasal congestion gets worse or lasts more than 5 days (children) or 7 days (adults) [bullet] fever gets worse or lasts more than 3 days [bullet] redness or swelling is present [bullet] new symptoms occur".

(4) *For permitted combinations containing an antihistamine combined with an oral antitussive.* The labeling states the warning "When using this product [in bold type] [bullet] may cause marked drowsiness." The word "marked" may be deleted from the warning upon petition under the provisions of § 10.30 of this chapter provided adequate data are submitted to demonstrate that the combination product does not cause a significant increase in drowsiness as compared with each active ingredient when tested alone. The petition and the data it contains will be maintained in a permanent file for public review in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

(5) *For permitted combinations containing camphor, menthol, and eucalyptus oil identified in § 341.40(u).* The labeling states the warnings for topical antitussive ingredients in § 341.74(c).

(6) *For permitted combinations containing levmetamfetamine with aromatics identified in § 341.40(v).* The labeling states the warnings for topical nasal decongestant ingredients in § 341.80(c)(2).

(d) *Directions.* The labeling of the product states, under the heading "Directions," directions that conform to the directions established for each ingredient in the directions sections of the applicable OTC drug monographs, unless otherwise stated in paragraph (d) of this section. When the time intervals or age limitations for administration of the individual ingredients differ, the directions for the combination product may not exceed any maximum dosage limits established for the individual ingredients in the applicable OTC drug monograph.

(1) *For permitted combinations containing an anesthetic/analgesic and/or a demulcent in a liquid dosage form identified in § 341.40(k), (s), (t), (w), (x), (y), (z), (aa), and (bb).* The labeling states "[optional, bullet] gargle, swish around, or keep in the mouth for at least 1 minute and then swallow. Do not spit out."

(2) *For permitted combinations containing camphor, menthol, and eucalyptus oil identified in § 341.40(u).* The labeling states the directions for topical antitussive ingredients in § 341.74(d).

(3) *For permitted combinations containing levmetamfetamine with aromatics identified in § 341.40(v).* The labeling states the directions for topical nasal decongestant ingredients in § 341.80(d)(2)(i) and (d)(2)(viii).

[67 FR 78170, Dec. 23, 2002, as amended at 71 FR 43362, Aug. 1, 2006]

EFFECTIVE DATE NOTE: At 70 FR 58977, Oct. 11, 2005, § 341.85 was amended by revising the headings in paragraphs (b)(2) and (b)(3) and by revising paragraph (b)(2)(ii), effective Apr. 11, 2007. For the convenience of the user, the revised text is set forth as follows:

§ 341.85 Labeling of permitted combinations of active ingredients.

* * * * *

(b)(2) *For permitted combinations containing an analgesic-antipyretic active ingredient identified in § 341.40(a), (c), (f), (g), (m), (q), and (r) when labeled for relief of hay fever/allergic rhinitis and/or nasal congestion symptoms.*

* * * * *

(ii) The indication(s) for the cough-cold ingredient(s) consists of the labeling for antihistamines in § 341.72(b)(1) or (b)(2) and/or nasal decongestants in § 341.80(b)(1)(ii), as appropriate, and the labeling for any other cough-cold combination. This labeling may

follow a separate bullet(s) or may be combined with the indication in paragraph (b)(2)(i) of this section.

(b)(3) *For permitted combinations containing an oral analgesic-antipyretic active ingredient identified in § 341.40(a), (c), (f), (g), (m), (q), and (r) when labeled for relief of general cough-cold symptoms and/or the common cold and for relief of hay fever/allergic rhinitis and/or nasal congestion symptoms.*

* * * * *

§ 341.90 Professional labeling.

The labeling of the product provided to health professionals (but not to the general public) may contain the following additional dosage information for products containing the active ingredients identified below:

(a) *For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, or racephedrine hydrochloride identified in § 341.16 (a), (b), (c), and (f).* Children 6 to under 12 years of age: oral dosage is 6.25 to 12.5 milligrams every 4 hours, not to exceed 75 milligrams in 24 hours. Children 2 to under 6 years of age: oral dosage is 0.3 to 0.5 milligram per kilogram of body weight every 4 hours, not to exceed 2 milligrams per kilogram of body weight in 24 hours.

(b) *For products containing chlophedianol hydrochloride identified in 341.14(a)(1).* Children 2 to under 6 years of age: oral dosage is 12.5 milligrams every 6 to 8 hours, not to exceed 50 milligrams in 24 hours.

(c) *For products containing codeine ingredients identified in § 341.14(a)(2).* (1) Children 2 to under 6 years of age: Oral dosage is 1 milligram per kilogram body weight per day administered in four equal divided doses. The average body weight for each age may also be used to determine dosage as follows: For children 2 years of age (average body weight, 12 kilograms), the oral dosage is 3 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours; for children 3 years of age (average body weight, 14 kilograms), the oral dosage is 3.5 milligrams every 4 to 6 hours, not to exceed 14 milligrams in 24 hours; for children 4 years of age (average body weight, 16 kilograms), the oral dosage is 4 milligrams every 4 to 6 hours, not to exceed 16 milligrams in 24 hours: for children 5 years of age (average body weight, 18 kilograms), the oral dosage is 4.5 milligrams every 4 to 6 hours, not to exceed 18 milligrams in 24 hours. The manufacturer must relate these dosages for its specific product dosages for its specific product to the use of the calibrated measuring device discussed in paragraph (c)(3) of this section. If age is used to determine the dose, the directions must include instructions to reduce the dose for low-weight children.

(2) Parents should be instructed to obtain and use a calibrated measuring device for administering the drug to the child, to use extreme care in measuring the dosage, and not exceed the recommended daily dosage.

(3) A dispensing device (such as a dropper calibrated for age or weight) should be dispensed along with the product when it is intended for use in children 2 to under 6 years of age to prevent possible overdose due to improper measuring of the dose.

(4) Codeine is not recommended for use in children under 2 years of age. Children under 2 years may be more susceptible to the respiratory depressant effects of codeine, including respiratory arrest, coma, and death.

(d) *The following labeling indication may be used for products containing guaifenesin identified in § 341.18 when used as a single ingredient product.* "Helps loosen phlegm and thin bronchial secretions in patients with stable chronic bronchitis."

(e) *For products containing brompheniramine maleate identified in § 341.12(a).* Children 2 to under 6 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours.

(f) *For products containing chlorcyclizine hydrochloride identified in § 341.12(b).* Children 6 to under 12 years of age: oral dosage is 12.5 milligrams every 6 to 8 hours, not to exceed 37.5 milligrams in 24 hours. Children 2 to under 6 years of age: oral dosage is 6.25 milligrams every 6 to 8 hours, not to exceed 18.75 milligrams in 24 hours.

(g) *For products containing chlorpheniramine maleate identified in § 341.12(c).* Children 2 to under 6 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours.

(h) *For products containing dexbrompheniramine maleate identified in § 341.12(d).* Children 2 to under 6 years of age: oral dosage is 0.5 milligram every 4 to 6 hours, not to exceed 3 milligrams in 24 hours.

(i) *For products containing dexchlorpheniramine maleate identified in § 341.12(e).* Children 2 to under 6 years: oral dosage is 0.5 milligram every 4 to 6 hours, not to exceed 3 milligrams in 24 hours.

(j) *For products containing diphenhydramine citrate identified in § 341.12(f).* Children 2 to under 6 years of age: oral dosage is 9.5 milligrams every 4 to 6 hours, not to exceed 57 milligrams in 24 hours.

(k) *For products containing diphenhydramine hydrochloride identified in § 341.12(g).* Children 2 to under 6 years of age: oral dosage is 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 mg in 24 hours.

(l) *For products containing doxylamine succinate identified in § 341.12(h).* Children 2 to under 6 years of age: oral dosage is 1.9 to 3.125 milligrams every 4 to 6 hours, not to exceed 18.75 milligrams in 24 hours.

(m) *For products containing phenindamine tartrate identified in § 341.12(i).* Children 2 to under 6 years of age: oral dosage is 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 milligrams in 24 hours.

(n) *For products containing pheniramine maleate identified in § 341.12(j).* Children 2 to under 6 years of age: oral dosage is 3.125 to 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 milligrams in 24 hours.

(o) *For products containing pyrilamine maleate identified in § 341.12(k).* Children 2 to under 6 years of age: oral dosage is 6.25 to 12.5 milligrams every 6 to 8 hours, not to exceed 50 milligrams in 24 hours.

(p) *For products containing thonzylamine hydrochloride identified in § 341.12(l).* Children 2 to under 6 years of age: oral dosage is 12.5 to 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours.

(q) *For products containing triprolidine hydrochloride identified in § 341.12(m).* Children 4 to under 6 years of age: oral dosage is 0.938 milligram every 4 to 6 hours, not to exceed 3.744 milligrams in 24 hours. Children 2 to under 4 years of age: oral dosage is 0.625 milligram every 4 to 6 hours, not to exceed 2.5 milligrams in 24 hours. Infants 4 months to under 2 years of age: oral dosage is 0.313 milligram every 4 to 6 hours, not to exceed 1.252 milligrams in 24 hours.

(r) *For products containing diphenhydramine citrate identified in § 341.14(a)(5).* Children 2 to under 6 years of age: oral dosage is 9.5 milligrams every 4 hours, not to exceed 57 milligrams in 24 hours.

(s) *For products containing diphenhydramine hydrochloride identified in § 341.14(a)(6).* Children 2 to under 6 years of age: oral dosage is 6.25 milligrams every 4 hours, not to exceed 37.5 milligrams in 24 hours.

[51 FR 35339, Oct. 2, 1986, as amended at 52 FR 30057, Aug. 12, 1987; 54 FR 8509, Feb. 28, 1989; 57 FR 58376, Dec. 9, 1992; 59 FR 4218, Jan. 28, 1994; 59 FR 29174, June 3, 1994; 59 FR 36051, July 15, 1994]

PART 343—INTERNAL ANALGESIC, ANTIPYRETIC, AND ANTIRHEUMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Subpart B—Active Ingredients

Subpart C—Labeling

Subpart D—Testing Procedures

AUTHORITY: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

SOURCE: 63 FR 56814, Oct. 23, 1998, unless otherwise noted.

2. References

REFERENCE 1

INTER-OFFICE MEMORANDUM

STERLING-WINTHROP RESEARCH INSTITUTE

RENSSELAER, NEW YORK

Ref 5

April 23, 1959

Memo to: Dr. Lands

From: F. P. Luduena

Subject: Comparative study of the effects of Neo-Synephrine HCl and Propadrine HCl on nasal air resistance (NAR), blood pressure and pulse rate of volunteers.

This study was carried out to provide information on the oral efficacy of Neo-Synephrine in comparison with Propadrine (memo from Dr. Tainter to Dr. Lands, Oct. 20, 1958).

Two series of experiments were carried out.(*) In one, the solutions were applied topically on the nasal mucosa. The blood pressure and the pulse rate were also determined in one of these experiments. In this case only one post-medication Nasal air resistance (NAR) reading was taken, one hour after medication. In the other three experiments, more frequent NAR readings were taken.

In the other series of experiments the drug was administered orally and blood pressure, pulse rate and NAR were determined before and one, two and five hours after drug administration.

Method. Nasal air resistance (NAR) was measured by the method of Sterntein and Schur (Arch. Otolaryngology, 23, 475, 1936). (A diagram of the apparatus used is shown in Fig. 1.) Each determination represents an average of 4 readings (2 with nosepiece in the right nostril and 2 with it on the opposite side) on the draft gauge.

Topical application. The solutions of Propadrine HCl (Merck, Sharp and Dohme, Inc.) in saline were prepared in the laboratory and placed in a sprayer similar to the container of Neo-Synephrine Nasal Spray (Winthrop Labs., Inc.). Applied to each nostril the container was squeezed three times. The average amount applied was approximately 0.5 cc. Four tests were run.

1) Propadrine HCl 0.5% was tested on 14 individuals. NAR, blood pressure and pulse rate were tested on the same volunteers. No changes were observed.

In the following three tests only NAR was determined. NAR readings were taken 5, 15, 60 and 180 minutes after drug application.

Propadrine HCl 1.0%: 24 individuals.

A reduction in NAR occurred within 5 minutes, reached

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(*) All the tests were carried out by Mrs. Ann Snyder.

its maximum at the 15-minute reading, was present at the 60-minute reading and disappeared within the next 2 hours.

Neo-Synephrine HCl 0.5%. (First N-S test): 14 individuals.

A rapid reduction in the NAR was observed after medication. The lowest NAR was obtained at the 15-minute reading. The effect was present one hour after medication but not at the 3-hr. reading.

Neo-Synephrine HCl 0.5%. (Second N-S test).

This test was run on the same 24 volunteers who were medicated with Propadrine HCl 1%. The maximal reduction in NAR was observed, as in the previous tests, at the 15-minute reading. (The lines obtained by plotting the mean draft gauge reading against time for the topical tests is shown in Chart 1. The average control readings of more than 100 tests are included. The mean draft gauge readings are also shown in Table 1.) (Frequency distributions are shown in Charts 2 and 3.)

Two methods were used to determine whether the differences observed were statistically significant: 1) Differences between means (mean reading before vs. mean reading after medication). 2) Differences between medians (before vs. after medication). The median test was used for estimation of significance (Siegel, Nonparametric Statistics, 1956, page 111). The word significant will be used hereinafter to indicate a difference where $P < 0.05$, or in other words, a result which has a probability of 1/20 or less of being due to chance.

The reduction of NAR obtained with Propadrine HCl 1.0% and Neo-Synephrine 0.5% was found to be significant by the two aforementioned methods.

Conclusions. Neo-Synephrine HCl 0.5% and Propadrine HCl 1.0%, sprayed into the nasal cavities in volunteers, produced a pronounced reduction in nasal air resistance within 15 minutes, which lasted more than 60 minutes and less than 180 minutes. The effect of the Propadrine solution was less pronounced than [illegible]. On this basis, Neo-Synephrine is somewhat more than twice as active as Propadrine as a topical nasal vasoconstrictor.

Oral Administration.

The following doses of Neo-Synephrine HCl were tested: 10, 25, 50 and 75 mg. Two doses of Propadrine were tested: 25 and 50 mg.

Each of the doses was run as a double-blind test with a placebo. The complete test was run on two consecutive days. The number of individuals on each test was either 14 or 15.

At about 9 a.m., after control readings of blood pressure, pulse rate and nasal air resistance, the drug (or placebo) was administered orally. Readings were taken 1, 2 and 5 hours after drug administration.

The average weight of the 15 volunteers was 128.8 lbs.; the range: 103 - 168. The age range was 20 - 46. The results are summarized in Tables 2, 3 and 4.

Effect on heart rate. The mean pulse rate (MPR) of the combined placebo tests is shown on the lower lines of Tables 2, 3 and 4. The MPR was 80.2 ± 1.32 at the 9 - 10 a.m. reading and decreased as shown in Table 1 to 75.6 ± 1.5 two hours later. In the afternoon, 5 hours after drug administration, it was 85.6 ± 1.15. These differences are significant.

The highest MPR's in the individuals receiving N-S or Propadrine were also obtained at the control and the 5-hr. readings. The lowest MPR reading (71.1 ± 2.38) in this study was observed at the 2-hr. reading after administration of 50 mg of Propadrine HCl. However, the difference between this value and the control MPR at the 2-hr. reading is not significant.

Blood pressure. Only minor changes in the average systolic pressure at the 1-hr. and the 2-hr. readings were observed.

Propadrine. After administration of 50 mg of Propadrine HCl there was a small but significant increase in systolic pressure at the 1-hr. and the 2-hr. readings. Two hours later it was slightly lower than the premedication systolic pressure. The changes in diastolic pressure were similar.

Neo-Synephrine HCl. The average systolic blood pressure in the volunteers who received 75 mg of Neo-Synephrine HCl was somewhat higher at the 1-hr. and the 2-hr. readings than before medication, or at the [illegible] reading after administration of the placebo or the mean 2-hr. reading for all the placebo tests. However, the difference was only of a few mm Hg and not significant.

Nasal air resistance. (NAR)

Nasal air resistance was expressed in terms of arbitrary draft gauge units. A great deal of variation was observed between individuals and between readings in the same individual.

The average NAR at the first reading (9 - 10 a.m.) was higher than at the two subsequent readings. However, the mean does not represent accurately the population of control readings as shown by the frequency distributions in Chart 1; the differences observed were due mainly to a few high draft gauge reading values. The Chart shows that in more than 60% of the individuals tested the reading was 10 or less. In 7 - 8% of the cases the minimal value of 2 was observed. This means that in the majority of cases there was no nasal congestion.

Effect of Propadrine. After the administration of 50 mg the average NAR decreased from 16.2 ± 5.4 to 5.2 ± 1.46 in 1 hr. and 4.64 ± 0.48 in 2 hrs. In comparison with the corresponding placebo results, the difference is significant only at the readings 1 hr. after administration, when using the mean ± s.e. for estimation of significance. However, the differences between medians are not significant at either reading.

Neo-Synephrine. An average reduction in NAR was observed 1 hr. after administration. However, this reduction is not significant whether the arithmetic means or the medians are compared, (drug vs. placebo).

Discussion. Experiments on volunteers have shown that Neo-Synephrine HCl in oral doses of 50 to 75 mg does not differ significantly from Propadrine HCl in oral doses of 25 to 50 mg in its effect on pulse rate, blood pressure and nasal air resistance. Increases in systolic and diastolic blood pressure, significant only in the case of Propadrine, were observed after administration of the higher doses of the two drugs. 50 mg of Propadrine HCl and 75 mg of Neo-Synephrine HCl appear to be the threshold oral doses in man. This conclusion, in regard to Neo-Synephrine, is in agreement with findings reported by other investigators. Tainter and Stockton (Amer. J. Med. Sci. 185, 832, 1933) found that the minimal effective oral dose of racemic Neo-Synephrine in man was approximately 120 mg, and that a dose of 2 mg of the levo-isomer was equivalent in potency to 3.5 mg of the racemate. The minimal pressor dose would be approximately 70 mg on this basis. Keys and Violante (J. Clin. Invest. 21, 1, 1942) obtained similar results; they found that "the threshold oral dosage was 40 to 60 mg in the average [illegible]

By other routes of administration, Propadrine is less active than Neo-Synephrine; in our experiments, Neo-Synephrine was somewhat more than twice as active topically. By intravenous injections in dogs and cats, Neo-Synephrine has been found 10 to 20 times more active than Propadrine (Lands, A. M., First Symp. on Chem. Biol. Correlation, 73, 1951). Greater biological stability may explain the slightly

greater oral effectiveness of Propadrine in comparison with Neo-Synephrine.

The increase in blood pressure induced by 50 mg Propadrine and the effect in man observed by Tainter and Stockton (loc. cit.) and Keys and Violante (loc. cit.) with doses similar to those used by us, are most likely due to an increase in peripheral resistance. In anesthetized dogs, various pressor amines, in doses which produced moderate increases in blood pressure, also produced nasal vasoconstriction (Lands et al., J.P.E.T. 83: 253, 1945). However, the vasoconstriction produced by threshold doses of Propadrine and Neo-Synephrine may not necessarily extend to the nasal mucosa. If it does, the effect may not be apparent because of the high variability in the control nasal air resistance readings. In other words, a more pronounced vasoconstrictor effect would be required to produce significant changes in the nasal air resistance readings.

Results reported by Tainter and Stockton bear some relationship with those discussed above. In their experiments a total subcutaneous dose of 10 mg/kg of Neo-Synephrine was required to produce a measurable degree of conjunctival vasoconstriction (estimated indirectly by the reduction or prevention of chemosis after topical application of mustard oil).

The majority of the subjects tested in our experiments had fairly patent nasal passages; in some cases hardly any further shrinkage of the nasal mucosa could be expected from drug administration. (Perhaps a more pronounced effect could be produced in individuals with congested nasal mucosa.). However, topical application of 0.5% Neo-Synephrine produced a clear-cut reduction in nasal air resistance.

It can be concluded, therefore, that the greatest observed reduction in NAR occurring after drug administration was less pronounced than that which followed the intranasal application of 0.5% Neo-Synephrine HCl.

No significant difference was observed between Propadrine and Neo-Synephrine in their effect on pulse rate, blood pressure and nasal air resistance when administered orally to volunteers.

F. P. Ludueña

fpl/jah
cc: Dr. Buchanan (2)
Dr. Tainter (2)
Dr. Wessinger
file (2)

Table 1

Exp. #	No. of sub-jects	Spray Medi-cation	Nasal Air Resistance Draft Gauge Readings									
			Control		5 minutes after medication		15 minutes after medication		60 minutes after medication		180 minutes after medication	
			mean ± s.e.	*	mean ± s.e.	*	mean ± s.e.		mean ± s.e.	*	mean ± s.e.	*
1	15	N-S 0.5%	13.5	6.0	5.4 ± 0.7	4.5	4.1 ± 0.4	3.5	5.3 ± 0.6	5.0	12.0 ± 4.0	6.0
2	14	Pr. 0.5%	10.6	6.5	---	---	---	---	10.1	6.25	---	---
3	24	N-S 0.5%	18.1	9.5	10.6 ± 4.3	5.25	4.2 ± 0.6	3.5	6.3 ± 0.8	5.25	12.7	12.0
4	24	Pr. 1%	13.4	10.63	9.9 ± 1.4	8.63	6.6 ± 0.7	5.75	7.8 ± 1.0	6.38	14.4	13.1

* median

N-S = Neo-Synephrine HCl; Pr. = Propadrine HCl

Table 4

ORAL ADMINISTRATION

Exp. #	No. of sub-jects	Drug	Dose mg	Effect on Pulse Rate (mean of readings ± standard error) Control	1 hour after medication	2 hours after medication	5 hours after medication
1	15	Neo-Synephrine HCl	10	80.3	78.0	74.9	86.3
	15	Placebo		80.9	78.5	75.9	88.4
2	15	Neo-Synephrine HCl	25	84.5	75.7	79.2	86.5
	15	Placebo		79.6	77.5	75.2	84.5
3	14	Neo-Synephrine HCl	50	79.0	72.0 ± 3.5	72.4 ± 2.9	84.3
	14	Placebo		82.0	78.3 ± 3.5	74.6 ± 2.3	86.0
4	14	Neo-Synephrine HCl	75	82.3	71.9 ± 3.4	74.4 ± 3.6	85.1
	14	Placebo		79.0	76.6	76.9	86.9
5	15	Propadrine HCl	25	81.6 ± 3.1	75.7 ± 2.5	75.3 ± 2.8	86.8 ± 3.1
	15	Placebo		78.3 ± 3.0	78.7 ± 2.5	76.4 ± 2.4	86.3 ± 2.8
6	14	Propadrine HCl	50	79.6	75.4 ± 3.1	71.1 ± 2.37	83.7
	14	Placebo		82.0	80.0 ± 2.06	75.0 ± 1.76	82.0
	80	Control Exp.		80.2	78.2	75.6	85.6
	87	Placebos					

Table

ORAL ADMINISTRATION

Exp.	No. of subjects	Drug	Dose mg	Effect on Blood Pressure Systolic/Diastolic			
				Control	1 hour after medication	2 hours after medication	5 hours after medication
1	15	Neo-Synephrine	10	115.5/78.1	109.5/74.0	110.4/77.5	113.5/74.8
	15	Placebo		114.8/78.4	109.7/75.5	114.3/77.7	113.2/75.5
2	15	Neo-Synephrine	25	116.0/77.1	115.3/77.9	112.7/76.9	118.7/77.9
	15	Placebo		115.2/79.5	116.0/78.3	111.6/77.3	114.3/75.5
3	14	Neo-Synephrine	50	113.6/77	117.7/79	116.6/78	115.6/74
	14	Placebo		114/77	113/77	114/77	115/74
4	14	Neo-Synephrine	75	111.9/72.9	116.6 ± 2.2/80.0	113.9 ± 2.4/77.3	115.3/73.6
	14	Placebo		114.6/75.1	113.3/75.6	111.4/74.4	116.3/72.4
5	15	Propadrine	25	114.7/76.3	114.9/78.3	115.5/78.7	114.3/73.5
	15	Placebo		115.1/77.7	119.7/80.0	116.5/80.7	117.1/76.4
6	14	Propadrine	50	114.3/75	122.4 ± 3.8/81	122.7 ± 3.2/81	111.7/73
	14	Placebo		113.3 ± 2.4/73	113.0 ± 2.1/75	114.6 ± 2.2/76	114.6 ± 1.9/73
	87	Placebos		114.5/76.8	114.1/76.9	113.7/77.3	115.1/74.6

Table 4

ORAL ADMINISTRATION

Exp. #	No. of subjects	Drug	Dose mg	Nasal Air Resistance Draft gauge readings: Control mean	Control *	1 hour after medication mean	1 hour after medication *	2 hours after medication mean	2 hours after medication *	5 hours after medication mean	5 hours after medication *
1	15 15	Neo-Synephrine HCl Placebo	10	12.0 9.0		13.2 7.9		11.8 9.0		7.7 8.2	
2	15 15	Neo-Synephrine HCl Placebo	25	10.0 7.2	6.0 5.0	5.2 ± 0.6 8.2	4.5 6.8	6.2 7.6	6.0 7.0	6.5 6.7	5.0 6.0
3	14 14	Neo-Synephrine HCl Placebo	50	12.1 13.8	8.5 8.1	8.0 10.6	7.3 9.7	8.6 8.0	5.3 6.3	10.6 12.4	7.9 7.8
4	14 14	Neo-Synephrine HCl Placebo	75	12.6 15.8	6.6 6.0	5.9 ± 1.6 9.5 ± 2.1	4.5 6.9	9.4 ± 3.5 12.8 ± 4.1	4.8 6.9	8.9 17.9	7.8 7.3
5	15 15	Propadrine HCl Placebo	25	8.8 7.1	4.5 5.5	5.4 ± 1.1 4.5 ± 0.8	3.4 3.3	4.5 ± 0.7 6.2 ± 2.4	3.4 3.8	6.7 5.0	3.9 3.8
6	14 14	Propadrine HCl Placebo	50	18.3 11.5	11.3 7.9	5.2 ± 1.5 13.8 ± 5.2	4.1 6.9	4.6 ± 0.5 12.2 ± 4.2	4.0 6.4	7.0 12.1	4.1 8.1
	30 57	Control Exp. Placebos		10.3		9.0 ± 0.8		9.8 ± 1.1		10.3	

* median

Table →

ORAL ADMINISTRATION

Exp. #	No. of subjects	Drug	Dose mg	Nasal Air Resistance Draft gauge readings							
				Control		1 hour after medication		2 hours after medication		5 hours after medication	
				mean	*	mean	*	mean	*	mean	*
1	15	Neo-Synephrine HCl	10	12.0		13.2		11.8		7.7	
	15	Placebo		9.0		7.9		9.0		8.2	
2	15	Neo-Synephrine HCl	25	10.0	6.0	5.2 ± 0.6	4.5	6.2	6.0	6.5	5.0
	15	Placebo		7.2	5.0	8.2	6.8	7.6	7.0	6.7	6.0
3	14	Neo-Synephrine HCl	50	12.1	8.5	8.0	7.3	8.6	5.3	10.6	7.9
	14	Placebo		13.8	8.1	10.6	9.7	8.0	6.3	12.4	7.8
4	14	Neo-Synephrine HCl	75	12.6	6.6	5.9 ± 1.6	4.5	9.4 ± 3.5	4.8	8.9	7.8
	14	Placebo		15.8	6.0	9.5 ± 2.1	6.9	12.8 ± 4.1	6.9	17.9	7.3
5	15	Propadrine HCl	25	8.8	4.5	5.4 ± 1.1	3.4	4.5 ± 0.7	3.4	6.7	3.3
	15	Placebo		7.1	5.5	4.5 ± 0.8	3.3	6.2 ± 2.4	3.8	5.0	3.3
6	14	Propadrine HCl	50	18.3	11.3	5.2 ± 1.5	4.1	4.6 ± 0.5	4.0	7.0	4.1
	14	Placebo		11.5	7.9	13.8 ± 5.2	6.9	12.2 ± 4.2	6.4	12.1	8.1
	30	Control Exp.		10.3		9.0 ± 0.8		9.8 ± 1.1	—	10.3	
	87	Placebos									

* median

Fig. 1

APPARATUS FOR MEASURING NASAL AIR RESISTANCE

(MODIFICATION of STERNSTEIN and SCHUR)

(ARCH. OTOLARYNG. 23:475, 1936)

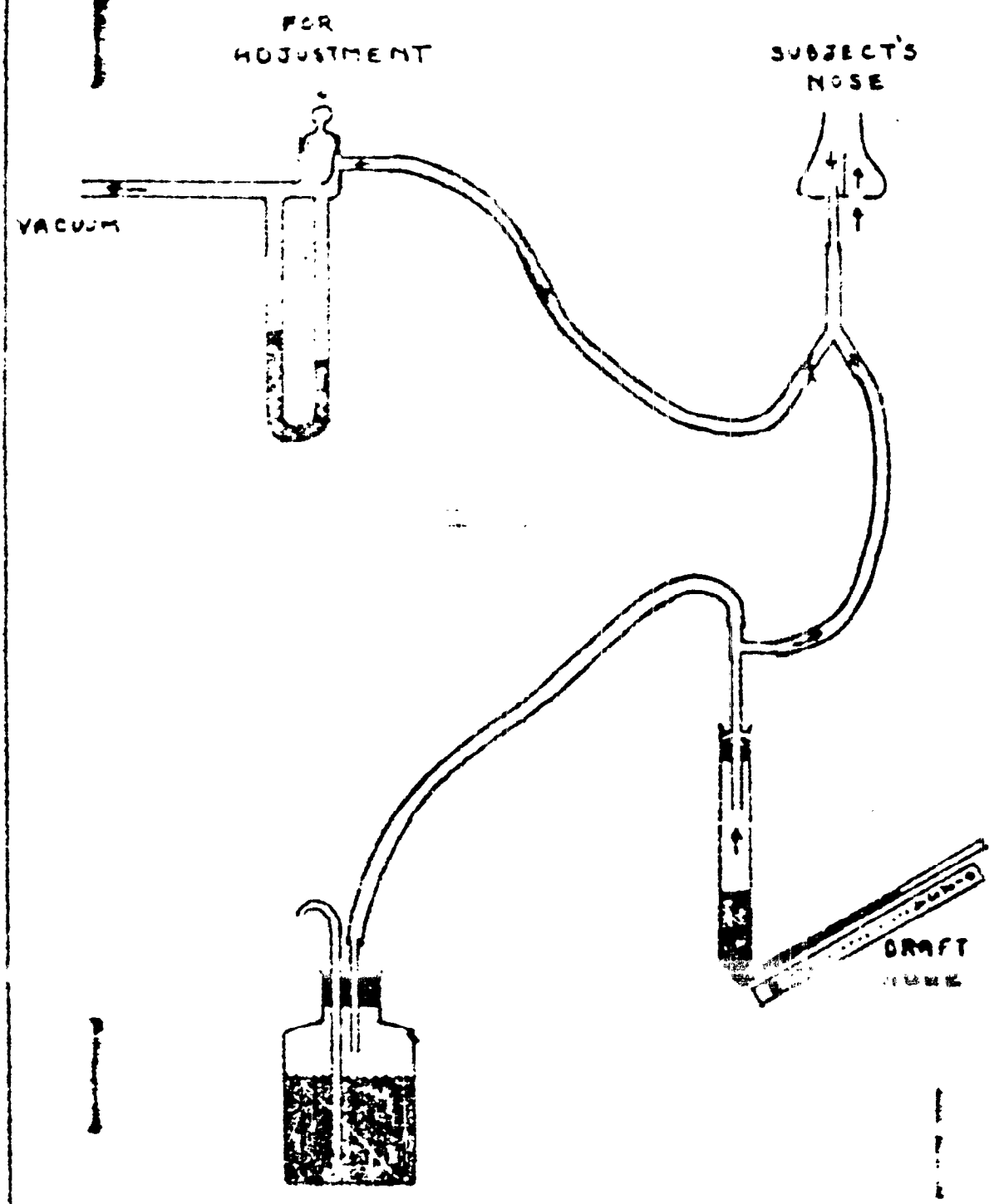


CHART 1

NASAL AIR RESISTANCE

DRAFT GAUGE READINGS

●●●●● PROPADRINE SPRAY 0.5%

——— PROPADRINE SPRAY 1%

– – – NEO-SYNEPHRINE SPRAY 0.5%

– – NEO-SYNEPHRINE SPRAY 1.0%

——— CONTROLS

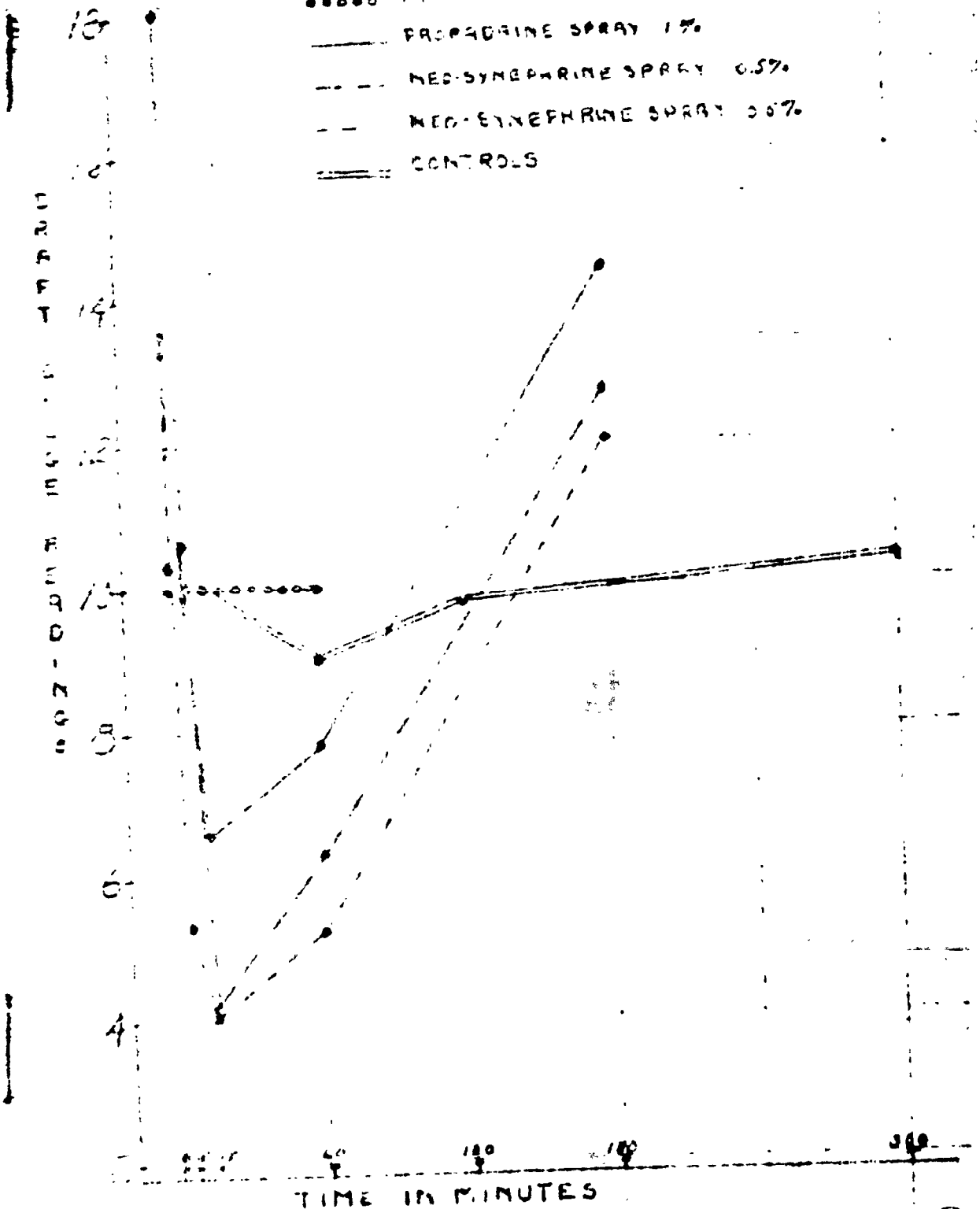
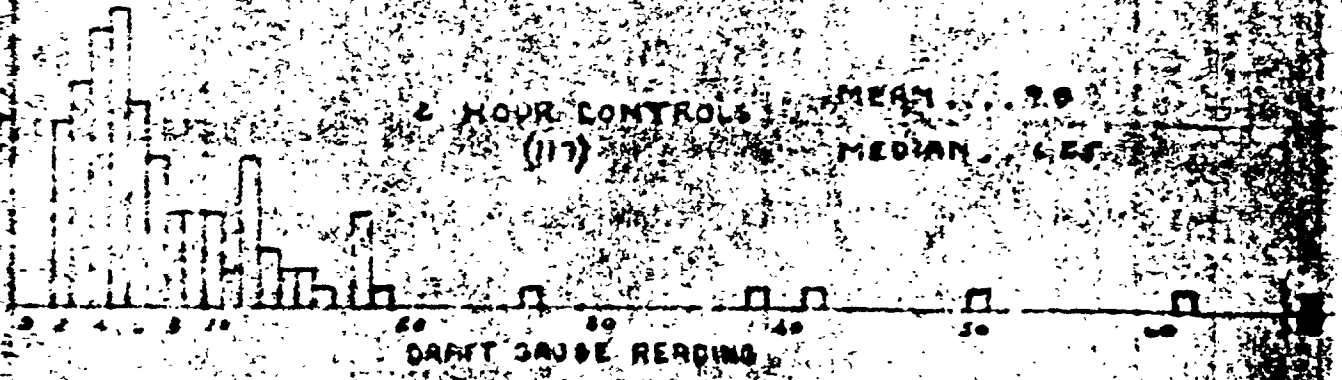
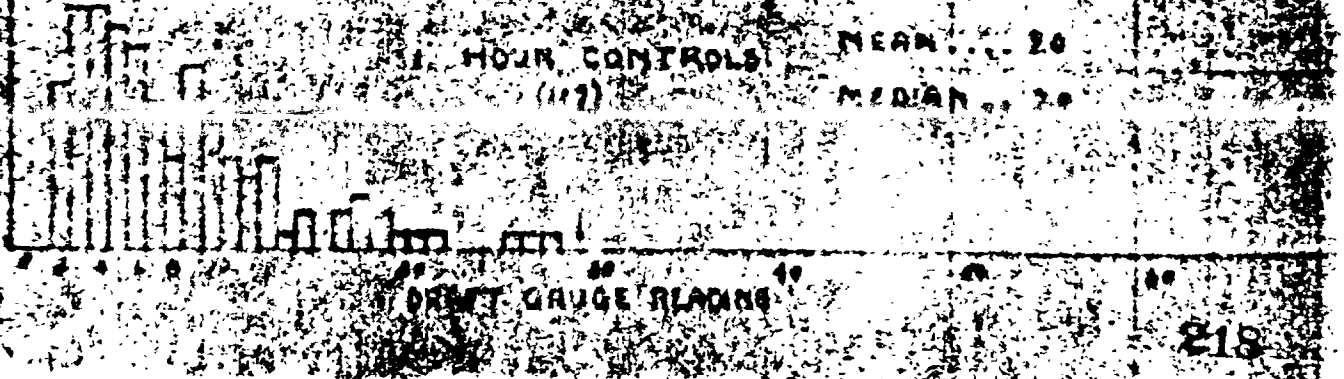


CHART 2

NASAL AIR RESISTANCE

FREQUENCY DISTRIBUTIONS





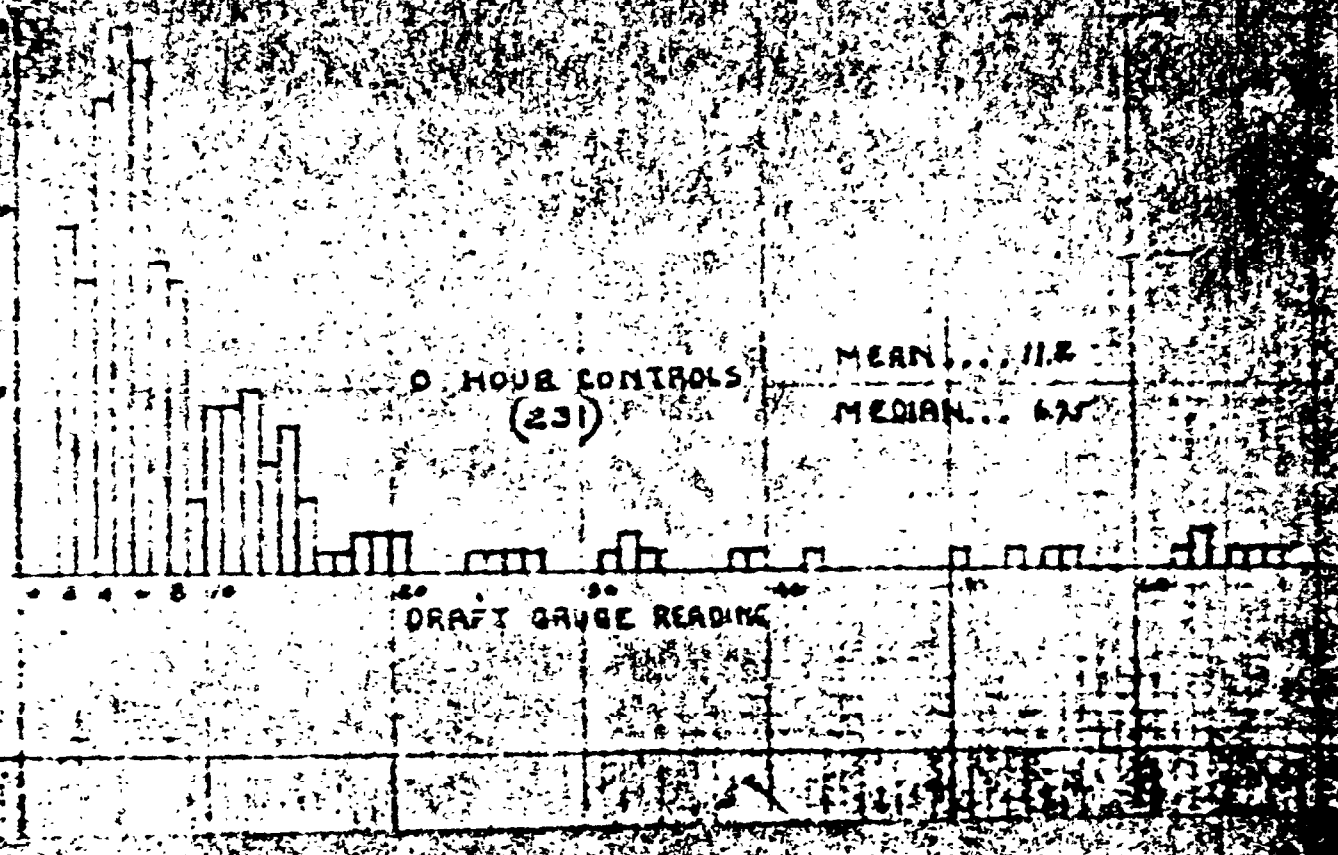
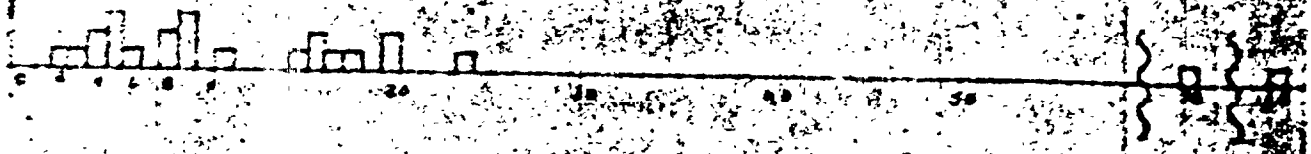

0 HOUR CONTROLS
(231)
MEAN... 11.8
MEDIAN... 6.5
DRAFT GAUGE READING

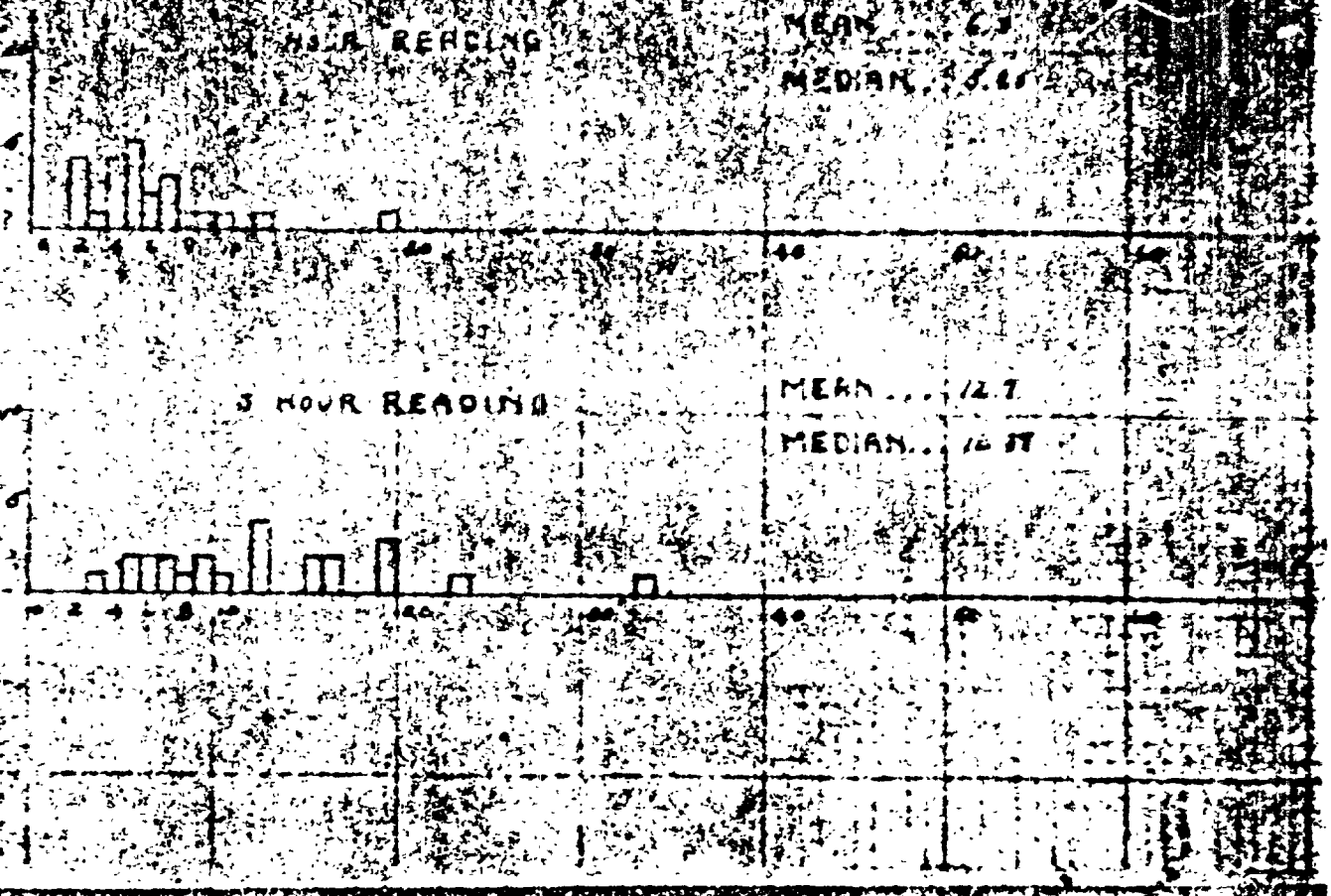
CHART 3

NASAL AIR RESISTANCE

FREQUENCY DISTRIBUTIONS

NEO-SYNEPHRINE NASAL SPRAY ½ %



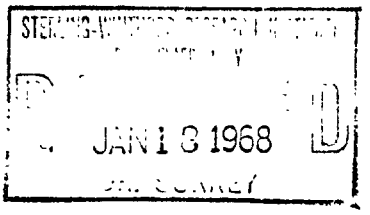

1 HOUR READING
MEAN ... 6.3
MEDIAN .. 5.65
3 HOUR READING
MEAN ... 12.7
MEDIAN .. 12.87

REFERENCE 2

INTER-OFFICE MEMORANDUM

STERLING-WINTHROP RESEARCH INSTITUTE

RENSSELAER, NEW YORK



January 12, 1968

To: Dr. Wessinger

From: N. A. Hulme

Re: Neo-Synephrine - Oral Study by Elizabeth Biochemical Labs No. 2

As a result of discussions within the Institute and with Winthrop Laboratories a second clinical study was set up with the Elizabeth Biochemical Laboratories for the purpose of further investigating the oral decongestant activity of Neo-Synephrine.

The results of an earlier study (Hulme to Suter 6-27-67) demonstrated that a single 25 mg oral dose of Neo-Synephrine produced significant decongestant effects in subjects having nasal congestion. Using this as a starting point, a protocol was devised in cooperation with Mr. Stander for the purpose of confirming this observation and dose ranging down to 10 mg, a level which has had acceptance for use in proprietary products. Also included in the study was a 50 mg dose of ephedrine sulfate for purposes of comparison with the maximum decongestant response expected under the conditions of this study.

Protocol and Methodology

A total of 38 volunteer subjects having demonstrable nasal congestion for two consecutive days participated in the study. The subjects were assigned the coded drugs on a double-blind randomized basis with the following number of subjects at each dose.

No. of Subjects	N-S vs. Placebo	Ephedrine vs. Placebo
16	10 mg	-
10	15 mg	-
6	25 mg	-
6	-	50 mg

The randomization was designed so that half of the subjects in each dose category received placebo on the first day and active medication on the second day. The reversed sequence occurred with the other subjects.

A modified Butler-Ivy airflow device built by the Institute and patterned after a similar instrument owned by the Vick's Corporation was used in this study.

Objective measurements were carried out by taking five nasal air resistance readings for each nostril at 0, 15 and 30 minute periods before medication and at 15, 30, 45, 60 and 120 minute intervals following medication. The five readings obtained from each nostril were combined and the means employed for analysis purposes.

At the time of each control and postmedication air resistance measurement each subject was asked to subjectively describe his congestion. This was recorded as being closest to one of the following statements and was scored as indicated.

Degree of Congestion	Score
Nose feels clear	0
Almost clear	1
Stuffy	2
Very stuffy	3
Completely blocked	4

Results

The air resistance measurement figures (see Appendix) were used to calculate arithmetic differences between premedication and postmedication results at indicated specific time intervals. These data were analyzed by Mr. Stander's group for significance between placebo and medication readings. The mean values and the degree of significance at each of the dosages are given in Table I. These data are also plotted as graphs for each dosage:placebo pair in Figures 1 to 4.

The scores recorded by the subjects as their impression of degree of congestion at premedication and postmedication time intervals were also analyzed by Mr. Stander's group and comparison made between placebo and active medication with the sum of the subjective impression differences. These differences, and the statistical significance between treatments for the drug:placebo pairs are given in Tables II to V.

Discussion

Objective evidence for increased nasal airflow was demonstrated for all medications. Assuming that a dose of 50 mg ephedrine produces a maximum response it is apparent from the graph that the decongestion effect of Neo-Synephrine at the 25 mg dose is also near maximum. The effect produced by both the 15 mg and 10 mg dosages is somewhat less than maximum. It is interesting to note that significant decongestion lasted for the full two hour measurement period for all dosages. A rapidity of onset was also apparent in that significant decongestion appeared at 15 minutes postmedication with both the 10 and 15 mg dosages. Failure to show significance at this time interval for the other two medications is most likely due to the small number of subjects (6) in each of these drug categories.

The analyses of the scores for the subjective impressions of decongestion showed a positive correlation for the 10 mg, 15 mg Neo-Synephrine and 50 mg ephedrine dosages but not for the 25 mg Neo-Synephrine dose. The latter may also be explained as due to the small number of subjects at that dose (6).

Conclusion

The primary purpose of the study, that is, to obtain information on oral activity of Neo-Synephrine over a range of dosages has been achieved. Significant decongestant activity for a single 10 mg dose of Neo-Synephrine when taken orally has been demonstrated by both objective and subjective tests.

Inasmuch as the evidence for oral decongestant activity is limited to the experience of one laboratory, it may be important to consider confirmation of this by another group. Additionally, it becomes apparent that more data are needed on the duration of effect and also on the lower limit of oral activity which at this point remains undetermined.

N. A. Hulme

bjc

cc: WPB > TEL > CL > CW
Mr. Stander
Dr. Cox
Dr. Surrey
Dr. Lands
Dr. Luduena
Dr. Gerding
Dr. Archer
File

Table I

COMPARISON OF THE NASAL DECONGESTANT EFFECT OF ORAL EPHEDRINE (50 mg) AND NEO-SYNEPHRINE (10 mg, 15 mg, and 25 mg) VERSUS PLACEBO IN SUBJECTS WITH "COMMON COLD"

Objective Measurements (units)

	t_0	$t_{15}-t_0$	$t_{30}-t_0$	$t_{45}-t_0$	$t_{60}-t_0$	$t_{90}-t_0$	$t_{120}-t_0$
Neo-Synephrine (10 mg)	13.4	-1.0	-2.8	-5.3	-5.3	-4.6	-3.6
Placebo	13.1	0.22	0.29	0.49	0.19	0.23	-0.075
Analysis of Variance Comparisons between treatments (n = 16)	p>0.05	p=0.01	p=0.01	p=0.01	p=0.01	p=0.05	p=0.01
Neo-Synephrine (15 mg)	12.4	-0.91	-3.0	-4.0	-4.8	-2.9	-2.3
Placebo	12.4	0.01	0.15	0.31	0.99	0.76	-0.36
Analysis of Variance Comparisons between treatments (n = 10)	p>0.05	p=0.01	p=0.01	p=0.01	p=0.01	p=0.01	p=0.05
Neo-Synephrine (25 mg)	13.6	-1.9	-6.3	-7.2	-6.6	-6.0	-5.3
Placebo	13.4	-0.73	-0.52	-0.067	0.38	0.03	-0.45
Analysis of Variance Comparisons between treatments (n = 6)	p>0.05	p>0.05	p=0.01	p=0.01	p=0.01	p=0.05	p=0.05
Ephedrine (50 mg)	13.2	-2.8	-5.5	-6.3	-7.3	-7.0	-5.4
Placebo	14.5	-0.63	-0.82	-0.85	-0.17	0.10	-0.73
Analysis of Variance Comparison between treatments (n = 6)	p>0.05	p>0.05	p=0.05	p=0.01	p=0.01	p=0.01	p=0.05

Fig. I COMPARISON OF THE NASAL DECONGESTANT EFFECT OF ORAL NEO-SYNEPHRINE® (10mg) AND PLACEBO IN 16 SUBJS. WITH "COMMON COLD"

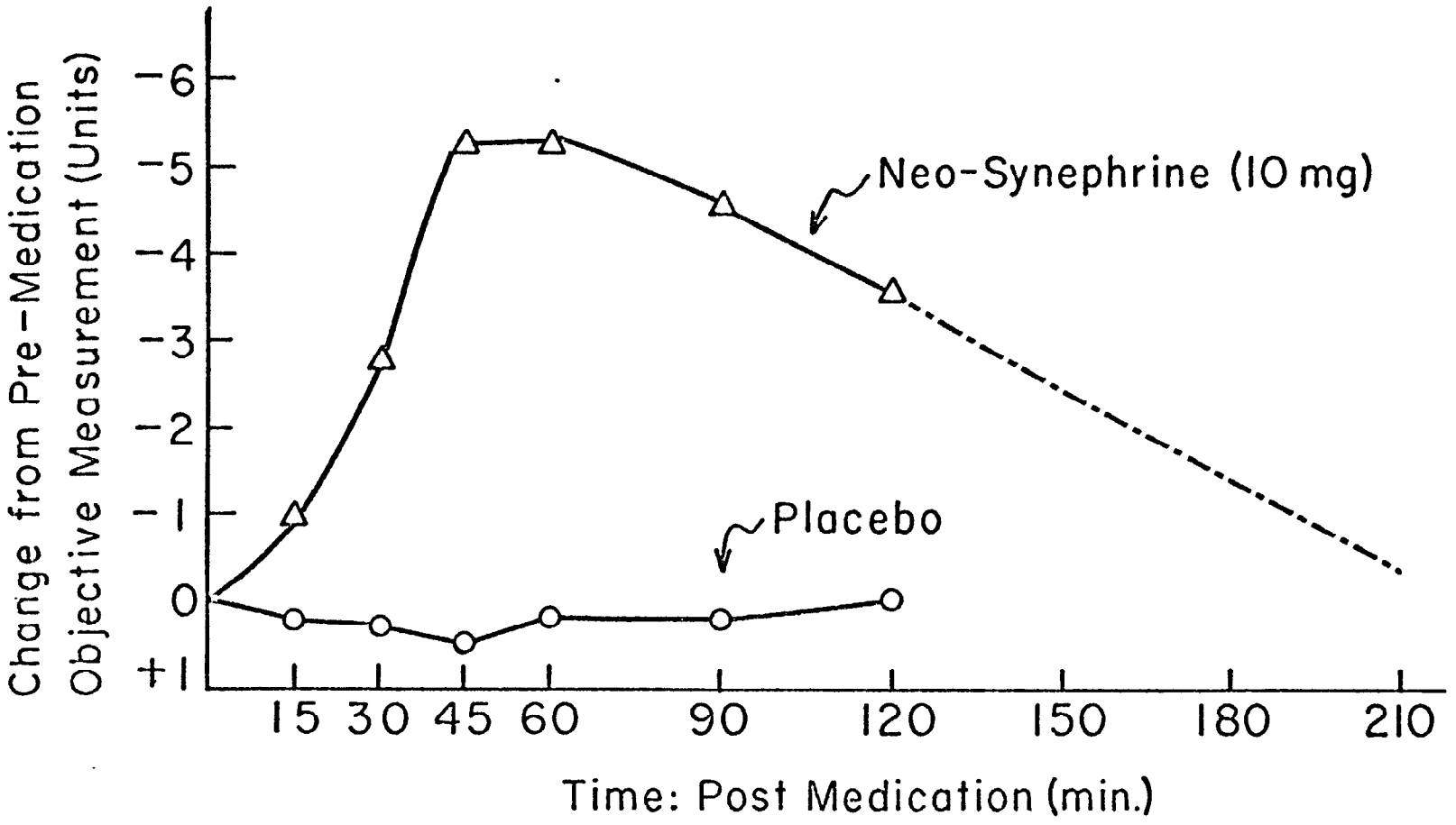


Fig. 2 COMPARISON OF THE NASAL DECONGESTANT EFFECT OF ORAL NEO-SYNEPHRINE® (15mg) AND PLACEBO IN 10 SUBJS. WITH "COMMON COLD"

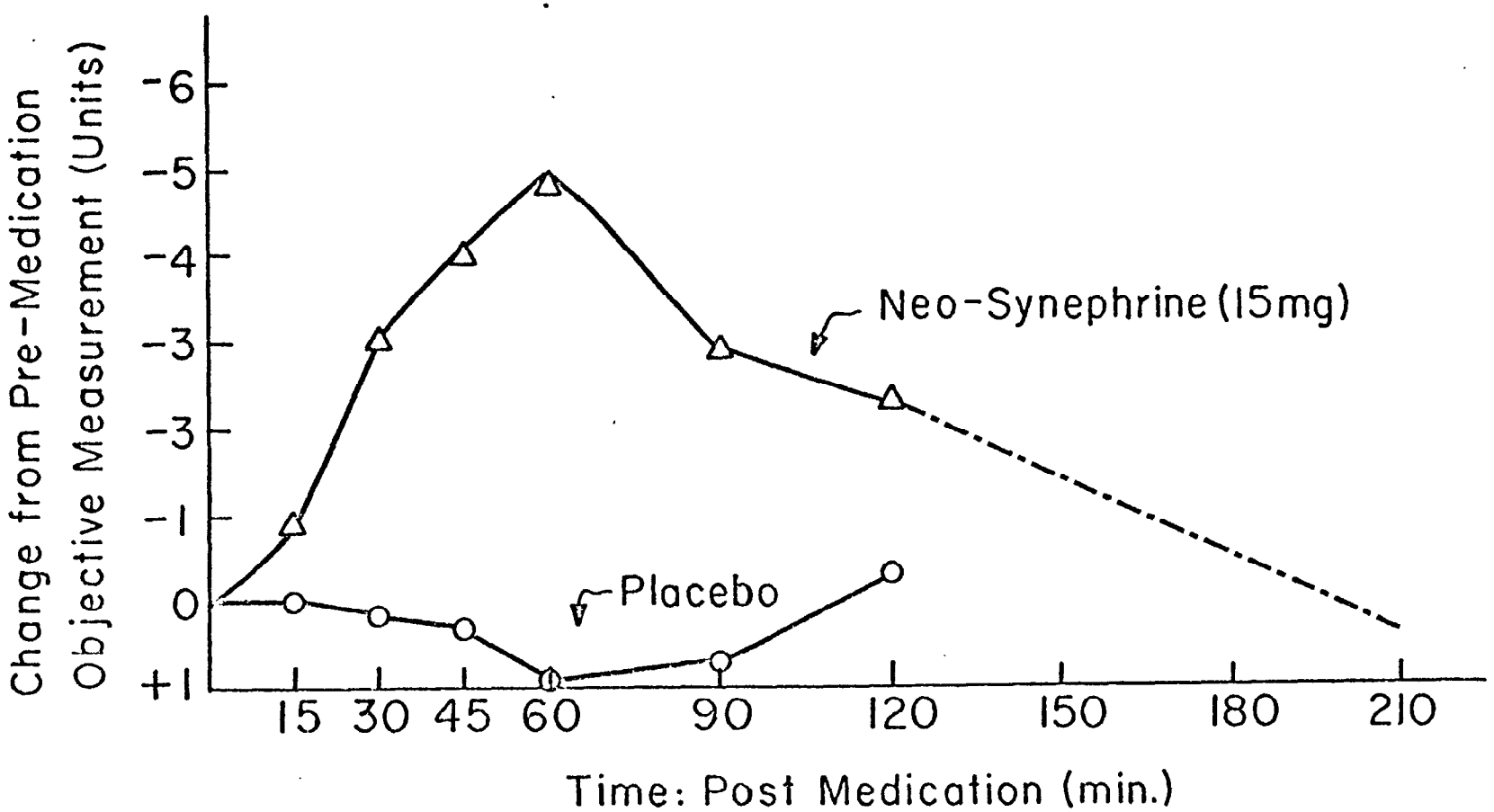


Fig. 3 COMPARISON OF THE NASAL DECONGESTANT EFFECT OF ORAL NEO-SYNEPHRINE® (25mg) AND PLACEBO IN 6 SUBJS. WITH "COMMON COLD"

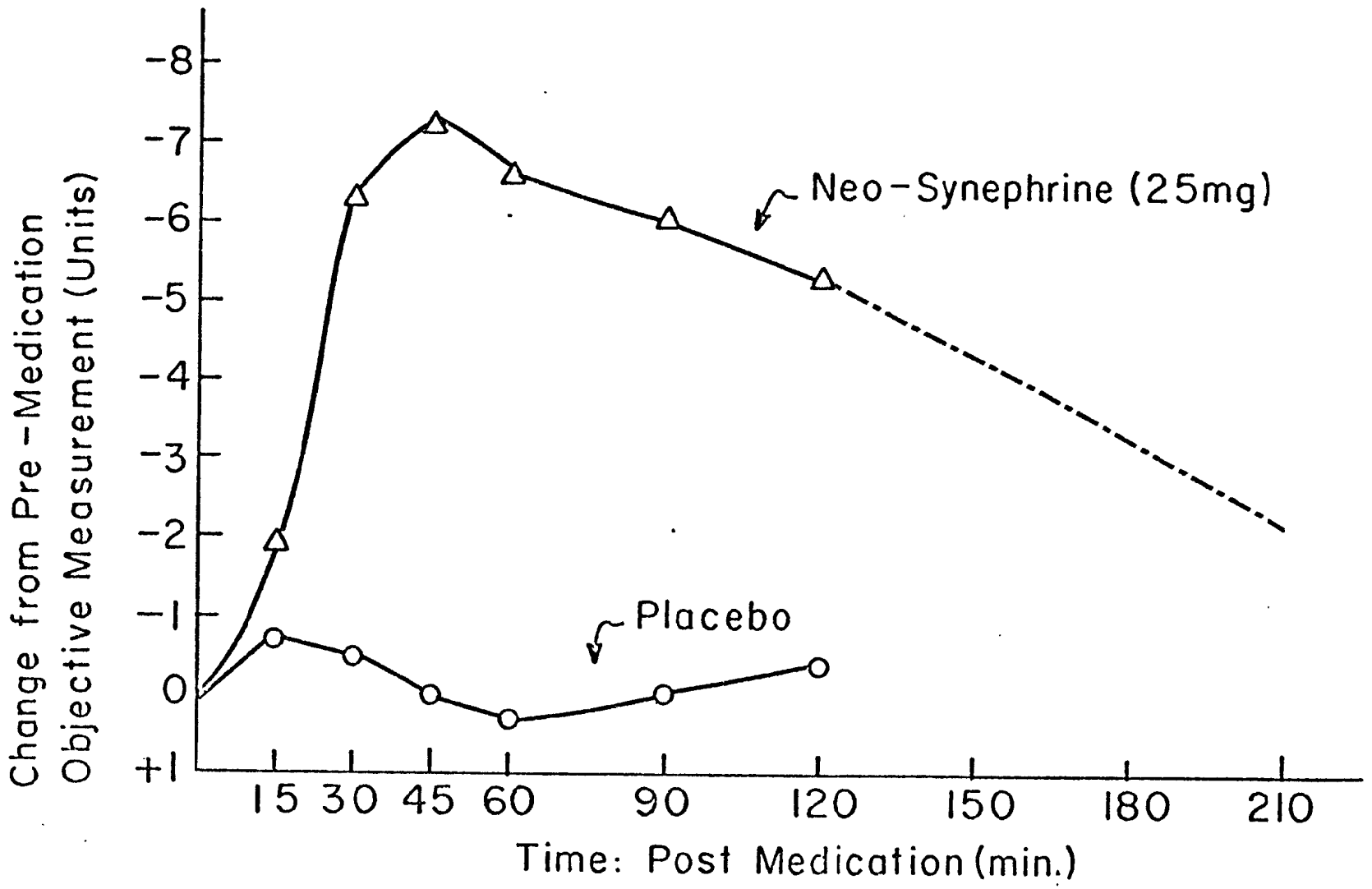


Fig. 4 COMPARISON OF THE NASAL DECONGESTANT EFFECT OF ORAL EPHEDRINE (50mg) AND PLACEBO IN 6 SUBJECTS WITH "COMMON COLD"

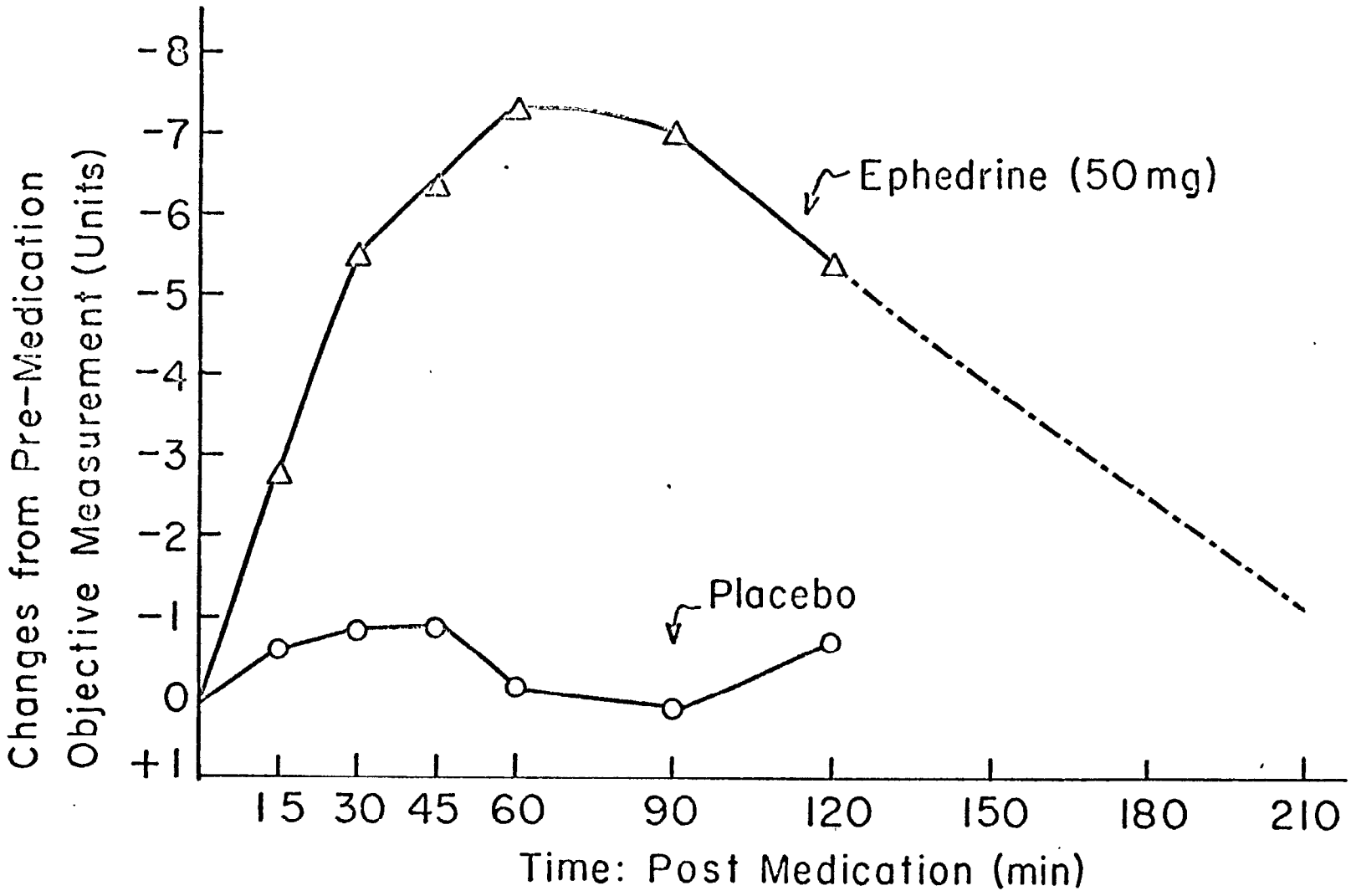


Table II

COMPARISON OF THE NASAL DECONGESTANT EFFECT OF ORAL NEO-SYNEPHRINE (10 mg) AND PLACEBO IN 16 SUBJECTS WITH "COMMON COLD"

Sum of the Subjective Impression Differences

Patient	Neo-Synephrine (10 mg)	Placebo
002	-5	-5
007	-11	-2
008	-5	-6
011	-4	-4
013	-2	-3
016	-13	-10
017	-5	-2
018	-12	-6
020	-12	-12
026	-9	-5
030	-7	-3
031	-5	+2
034	-7	-1
035	-6	-1
037	-4	0
038	-11	0
Median	-6	0

Significance of the difference between treatments; p=0.01
Wilcoxon Matched-Pairs Signed-Ranks test

Table III

COMPARISON OF THE NASAL DECONGESTANT EFFECT
OF ORAL NEO-SYNEPHRINE (15 mg) AND PLACEBO
IN 10 SUBJECTS WITH "COMMON COLD"

Sum of the Subjective Impression Differences

Patient	Neo-Synephrine (15 mg)	Placebo
001	-5	-3
004	-5	-5
005	-17	-1
014	-7	-3
019	-7	-3
021	-7	-8
024	-10	-3
027	+2	+1
033	-6	0
036	-4	0
Median	-6	-3

Significance of the difference between treatments; p=0.01
Wilcoxon Matched-Pairs Signed-Ranks test

Table IV

COMPARISON OF THE NASAL DECONGESTANT EFFECT
OF ORAL NEO-SYNEPHRINE (25 mg) AND PLACEBO
IN 6 SUBJECTS WITH "COMMON COLD"

Sum of the Subjective Impression Differences

Patient	Neo-Synephrine (25 mg)	Placebo
003	-14	-8
009	-9	-1
012	-12	-4
022	-6	-8
023	-11	-2
029	-9	-7
Median	-10	-6

Significance of the difference between treatments; $p>0.05$
Wilcoxon Match-Pairs Signed-Ranks test

Table V

COMPARISON OF THE NASAL DECONGESTANT EFFECT
OF ORAL EPHEDRINE SULFATE (50 mg) AND PLACEBO
IN 6 SUBJECTS WITH "COMMON COLD"

Sum of the Subjective Impression Differences

Patient	Eph. Sulfate (50 mg)	Placebo
006	-6	-5
010	-16	0
015	-23	-4
025	-6	-5
028	-6	-5
032	-11	-8
Median	-8	-5

Significance of the difference between treatments; p=0.05
Wilcoxon Match-Pairs Signed-Ranks test

APPENDIX

Objective Measurement Means*

Neo-Synephrine (10 mg)

Patient	Treatment	t_0	t_{15}	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}
002	Neo-Synephrine	10.5	7.0	5.0	5.5	4.3	3.6	3.1
	Placebo	10.7	10.3	11.5	10.3	10.9	12.1	10.5
007	Neo-Synephrine	11.0	11.1	6.0	6.9	5.1	6.1	8.9
	Placebo	11.3	11.0	11.4	11.5	11.4	11.7	11.8
008	Neo-Synephrine	12.7	11.1	10.8	6.4	7.3	8.0	8.6
	Placebo	17.3	17.1	16.6	17.5	17.3	16.4	16.6
011	Neo-Synephrine	10.6	10.6	9.9	7.3	8.0	10.0	9.3
	Placebo	11.7	10.6	11.5	12.1	11.9	11.1	9.7
013	Neo-Synephrine	11.3	9.5	7.9	8.5	6.1	7.0	8.9
	Placebo	10.5	11.5	11.3	11.6	12.6	13.0	10.5
016	Neo-Synephrine	17.5	17.0	14.0	10.9	12.0	12.0	15.2
	Placebo	14.9	15.5	14.9	15.0	15.4	14.3	15.1
017	Neo-Synephrine	13.9	13.0	8.6	7.5	6.8	8.2	14.1
	Placebo	13.5	13.5	14.0	14.0	13.5	15.3	13.8
018	Neo-Synephrine	14.6	14.5	12.6	10.7	7.5	8.2	9.8
	Placebo	13.9	14.1	13.3	14.0	12.9	14.0	13.1
020	Neo-Synephrine	19.5	19.7	17.3	9.6	8.5	9.5	9.6
	Placebo	13.6	14.0	14.1	14.0	13.9	13.5	14.3
026	Neo-Synephrine	17.5	15.5	13.0	7.5	9.1	11.3	10.5
	Placebo	15.7	16.5	15.7	14.5	14.7	16.0	16.9
030	Neo-Synephrine	11.6	10.6	10.9	6.9	11.6	11.7	11.0
	Placebo	14.5	14.5	14.5	14.8	12.6	12.1	13.5
031	Neo-Synephrine	12.5	12.7	9.1	7.9	9.9	11.2	9.5
	Placebo	11.8	11.9	12.1	14.0	12.5	9.5	8.9
034	Neo-Synephrine	13.5	11.5	11.0	7.4	7.3	7.2	9.5
	Placebo	12.3	12.8	13.5	14.0	13.0	14.0	13.0
035	Neo-Synephrine	14.0	12.2	12.1	6.9	6.4	7.5	7.5
	Placebo	13.6	14.5	14.1	14.0	13.6	14.5	14.6
037	Neo-Synephrine	11.5	11.0	10.4	9.1	7.0	7.5	9.5
	Placebo	12.5	12.7	13.0	13.4	14.3	13.9	12.4
038	Neo-Synephrine	12.6	11.5	10.5	9.0	10.8	11.4	11.6
	Placebo	11.4	12.3	12.3	12.4	11.7	11.5	13.3

*Each number represents the mean of 5 measurements on both right and left nostrils.

APPENDIX

Objective Measurement Means*

Neo-Synephrine (15 mg)

Patient	Treatment	t_0	t_{15}	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}
001	Neo-Synephrine	11.3	10.6	9.4	7.5	6.0	11.7	11.5
	Placebo	11.1	11.8	11.5	12.0	13.0	12.8	11.8
004	Neo-Synephrine	10.5	9.7	7.4	7.0	6.1	7.6	8.7
	Placebo	11.2	10.4	11.3	11.4	14.7	13.5	10.4
005	Neo-Synephrine	13.7	11.6	9.1	7.7	7.5	9.4	8.1
	Placebo	12.5	11.7	12.9	12.6	12.6	13.5	11.3
014	Neo-Synephrine	15.3	14.0	9.5	8.0	9.5	10.2	14.5
	Placebo	14.6	14.5	14.4	14.6	15.5	15.5	15.0
019	Neo-Synephrine	12.1	11.9	11.0	9.1	6.4	10.5	10.7
	Placebo	12.5	12.6	11.5	12.5	12.3	13.1	11.9
021	Neo-Synephrine	11.1	11.5	9.5	8.9	7.6	8.6	8.9
	Placebo	12.5	12.3	12.1	13.5	14.3	13.5	14.5
024	Neo-Synephrine	12.5	9.0	7.5	7.5	7.4	10.1	11.4
	Placebo	13.5	13.6	12.4	13.4	14.5	12.7	12.5
027	Neo-Synephrine	10.9	12.1	12.5	11.7	11.7	11.4	8.4
	Placebo	12.9	13.5	14.0	12.0	12.1	12.6	10.5
033	Neo-Synephrine	10.5	9.6	7.3	7.5	5.9	5.9	5.6
	Placebo	10.7	11.7	12.0	12.4	12.8	12.5	11.3
036	Neo-Synephrine	15.8	14.6	10.5	8.9	7.1	9.0	12.7
	Placebo	12.5	12.0	13.4	12.7	12.1	11.9	11.2

*Each number represents the mean of 5 measurements on both right and left nostrils.

APPENDIX

Objective Measurement Means*

Neo-Synephrine (25 mg)

Patient	Treatment	t_0	t_{15}	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}
003	Neo-Synephrine	17.5	13.5	7.6	6.5	5.5	5.9	5.5
	Placebo	10.2	10.1	10.3	9.5	10.9	10.5	10.4
009	Neo-Synephrine	11.7	8.9	5.4	4.9	5.3	6.9	8.9
	Placebo	11.5	11.7	10.1	11.8	12.2	12.0	11.2
012	Neo-Synephrine	14.4	12.5	6.5	6.1	7.6	6.1	10.4
	Placebo	13.6	12.0	11.8	13.3	13.0	12.5	13.8
022	Neo-Synephrine	12.5	11.0	8.4	9.5	10.9	11.5	10.6
	Placebo	15.1	13.4	14.0	13.5	14.5	14.0	14.4
023	Neo-Synephrine	12.8	11.4	7.4	6.1	6.3	6.5	5.5
	Placebo	9.5	11.0	11.6	12.1	12.4	12.5	10.1
029	Neo-Synephrine	12.7	12.9	8.4	5.0	6.1	8.7	9.0
	Placebo	20.7	18.0	19.7	20.0	19.9	19.3	18.0

*Each number represents the mean of 5 measurements on both right and left nostrils.

APPENDIX

Objective Measurement Means*

Ephedrine Sulfate (50 mg)

Patient	Treatment	t_0	t_{15}	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}
006	Eph. Sulfate	11.5	7.8	4.0	3.5	3.2	4.5	3.2
	Placebo	12.3	11.8	10.5	11.2	12.0	13.9	11.8
010	Eph. Sulfate	15.1	8.7	4.5	5.5	6.0	5.9	4.5
	Placebo	11.4	11.4	12.1	11.0	12.0	12.0	11.3
015	Eph. Sulfate	18.4	16.1	13.9	10.8	9.2	10.0	15.9
	Placebo	19.1	19.3	17.2	16.7	18.0	19.5	19.6
025	Eph. Sulfate	11.0	8.9	7.3	6.8	5.5	4.5	4.7
	Placebo	13.1	12.0	13.2	12.5	13.1	12.0	11.4
028	Eph. Sulfate	12.1	10.4	8.9	7.5	6.4	5.9	7.6
	Placebo	12.1	12.0	11.3	11.5	11.9	11.6	12.5
032	Eph. Sulfate	11.1	10.7	7.4	7.1	5.0	6.1	10.8
	Placebo	18.9	16.6	17.7	18.9	18.9	18.5	15.9

*Each number represents the mean of 5 measurements on both right and left nostrils.

STERLING-WINTHROP RESEARCH INSTITUTE cc: Dr. Wessinger
RENSSELAER, NEW YORK File

COPY FOR [redacted]
DR. WESSINGER

March 18, 1968 Vol 169 V-A-T

Ref #7

To: Dr. N. A. Hulme (2)

From: H. Stander

Subject: Neo-Synephrine Oral Study/Elizabeth Biochemical Laboratories (No. 2)

This report is submitted as an addendum to your memorandum of January 12, 1968, (Hulme to Wessinger) on the above noted subject. It includes an analysis of objective measurements of nasal air resistance taken 0, 15, and 30 minutes prior to medication. Of these sampling times, only the reported 0 minutes prior to medication measurements were employed in evaluating the effect of Neo-Synephrine and placebo treatments on nasal air resistance.

The consistency of pretreatment measurements, as well as the basis for referring post-treatment measurements to the time 0 reading is apparent from an analysis of the test data tabulated in the appendix. Means of five readings from left to right nostrils, for the 38 volunteer subjects tested on two successive days, were analyzed. The analysis shows the following: (see tables 1 and 2)

1. As expected, there was a highly significant difference among patients on either the first or second day of testing. Since each patient served as his own control, and received both placebo and medication, the effect of this difference on treatment contrasts could be considered minimal.

2. There was also a highly significant difference among patient responses over the 0, 15, and 30 minutes premedication time periods, with a consistent trend toward increased nasal air resistance as related to time of observation. The fact that the trend was consistent led to the selection of the measurement just prior to medication as the "best" estimate of the patients premedication condition.

3. An apparent difference between right and left nostril was observed on the first day of testing. On the second test day the difference between right and left nostril, though still present, varied significantly with respect to subjects. Some subjects showed greater resistance with the left nostril than with the right, and some showed greater resistance with the right nostril than with the left. For the analysis of the treatment data, "hidden replication" was employed; that is, the results from both nostrils as well as repeat observations within a nostril were averaged to provide a single estimate of a subject's nasal air resistance.

4. The standard deviation of a nasal air resistance observation, as tabulated in the appendix, was estimated as approximately 0.5 units.

bjc

H. Stander

Table 1

Analysis of Variance: First Day of Medication Results

Source	d.f.	ms	F
Total	227		
Patients	37	40.6648	195.5978**
Times	2	17.2650	83.0447**
Positions	1	1.21	5.8201*
Pts x Times	74	0.4185	2.0129
Times x Pos.	2	0.5150	2.4771
Pts. x Pos.	37	0.2332	1.1216
Pts x Pos. x Times	74	0.2079	

s = 0.46 units

Table 2

Analysis of Variance: Second Day of Medication Results

Source	d.f.	ms	F
Total	227		
Patients	37	27.3367	30.7741**
Times	2	13.15	48.8121**
Positions	1	1.21	1.3621
Pts x Times	74	0.4378	1.6250
Times x Pos.	2	0.7600	2.8210
Pts. x Pos.	37	0.8883	3.2973**
Pts x Pos. x Times	74	0.2694	

s = 0.52 units

*significant, p = 0.05
**significant, p = 0.01

APPENDIX

First Day of Medication Results

(units)

Patient	t=30 minutes before medication		t=15 minutes before medication		t=0 minutes before medication	
	Left Nostril	Right Nostril	Left Nostril	Right Nostril	Left Nostril	Right Nostril
1	10.4	11.0	11.0	11.4	11.2	11.4
2	10.0	9.8	10.6	10.8	10.8	10.6
3	16.6	16.4	17.4	16.6	17.4	17.6
4	9.8	9.4	10.0	9.8	10.6	10.4
5	10.6	11.6	12.4	12.6	12.4	12.6
6	11.6	11.4	12.6	11.8	12.4	12.2
7	10.6	11.2	10.8	11.4	11.4	11.2
8	11.6	11.2	11.6	12.4	12.8	12.6
9	10.2	10.4	10.6	11.4	11.6	11.4
10	13.6	14.6	14.6	15.2	14.8	15.4
11	9.8	10.8	11.6	11.2	11.6	11.8
12	14.2	15.2	14.4	14.6	14.2	11.6
13	9.6	9.6	10.6	11.6	11.2	11.4
14	14.4	14.6	14.6	14.6	15.4	15.2
15	18.2	18.6	18.8	18.6	18.4	18.6
16	17.6	16.4	17.6	16.6	17.6	17.4
17	12.4	12.8	12.6	13.2	13.6	13.4
18	12.4	12.8	13.6	12.6	13.4	14.4
19	10.4	11.2	11.2	11.6	11.8	12.4
20	18.4	18.4	19.6	19.8	19.4	19.6
21	12.4	12.6	12.6	12.4	12.6	12.4
22	15.2	15.4	15.6	15.4	15.6	14.6
23	11.8	12.4	12.4	12.6	12.8	12.8
24	11.4	11.2	11.6	11.8	12.4	12.6
25	11.4	11.6	11.8	12.2	12.8	13.4
26	15.4	16.4	16.6	15.8	15.6	15.8
27	10.2	10.4	12.8	12.6	12.4	13.4
28	10.4	10.6	11.2	11.4	11.6	12.6
29	18.4	19.4	19.2	21.2	20.6	20.8
30	13.4	13.8	13.6	14.4	14.4	14.6
31	10.6	11.4	12.6	11.6	12.4	12.6
32	17.4	16.4	17.6	17.6	19.4	18.4
33	10.6	10.4	11.2	10.4	10.6	10.8
34	11.4	11.4	13.4	13.6	12.6	14.4
35	12.6	14.6	14.4	13.6	13.8	14.2
36	10.4	10.4	11.6	11.4	12.6	12.4
37	11.6	12.6	12.4	12.6	12.4	12.6
38	12.2	13.4	13.4	12.4	12.4	12.8
	12.6	12.9	13.4	13.4	13.7	13.7

APPENDIX

Second Day of Medication Results

(units)

	t=30 minutes before medication		t=15 minutes before medication		t=0 minutes before medication	
Patient	Left Nostril	Right Nostril	Left Nostril	Right Nostril	Left Nostril	Right Nostril
1	10.6	10.8	11.8	11.4	11.2	11.0
2	9.4	9.2	10.4	9.8	10.6	10.4
3	10.2	9.8	9.6	9.8	10.4	10.0
4	10.0	10.4	10.2	10.4	10.8	11.6
5	12.4	12.6	12.6	13.4	13.6	13.8
6	11.2	10.6	11.6	11.8	11.6	11.4
7	9.6	9.8	10.4	10.6	11.2	10.8
8	16.4	17.2	17.4	17.6	17.4	17.2
9	10.4	11.4	10.6	11.6	11.8	11.6
10	10.4	10.4	10.6	10.4	11.4	11.4
11	9.8	11.2	10.8	10.6	10.8	10.4
12	12.6	12.8	13.4	13.6	13.8	13.4
13	10.6	9.6	11.2	11.4	10.6	10.4
14	13.6	12.6	14.2	14.4	14.6	14.6
15	14.8	20.6	16.6	20.6	17.6	20.6
16	14.6	14.6	15.6	14.6	14.4	15.4
17	13.6	13.8	13.4	14.4	14.4	13.4
18	12.6	13.4	13.4	14.6	14.4	14.8
19	11.4	10.4	11.4	11.4	12.4	12.6
20	13.4	13.2	13.6	13.8	13.6	13.6
21	10.6	10.6	10.4	10.6	10.6	11.6
22	12.6	11.4	12.4	12.6	12.4	12.6
23	9.8	9.6	10.6	9.8	9.4	9.6
24	11.4	11.6	12.4	14.4	14.4	12.6
25	9.2	8.4	10.4	11.4	11.4	10.6
26	15.2	15.4	16.4	17.4	17.6	17.4
27	9.6	9.6	9.8	10.6	10.6	11.2
28	10.6	12.6	12.4	12.4	11.6	12.6
29	14.4	12.6	12.8	13.2	12.6	12.8
30	11.2	11.6	11.4	11.6	11.8	11.4
31	9.6	9.4	11.4	12.6	12.4	11.2
32	9.6	9.4	11.2	10.4	11.6	10.6
33	10.4	9.4	10.6	11.2	10.4	10.6
34	12.4	12.4	12.8	12.6	12.4	12.2
35	12.8	12.6	13.4	13.6	13.4	13.8
36	15.4	15.6	16.6	16.4	16.4	15.2
37	11.6	12.6	12.2	11.4	11.6	11.4
38	12.4	12.2	11.6	12.6	11.6	11.2
	11.7	11.9	12.3	12.7	12.6	12.6

REFERENCE 3

STERLING-WINTHROP RESEARCH INSTITUTE

MEDICAL RESEARCH DIVISION

May 27, 1970

To: Dr. Blackmore

From; N. A. Hulme

Re: Neo-Synephrine - Elizabeth Bio-Chemical Laboratory Study No. 5

This was the fifth in a series of nasal decongestant studies carried out by the Elizabeth Bio-Chemical Laboratory. The results of previous studies by this group have been consistent in demonstrating statistically significant differences between placebo and Neo-Synephrine at various dosages administered orally to subjects with proven nasal congestion. The dosages used in this study were those recommended at the May 19, 1969, Medical Research Conference.

This study as originally planned was to have been conducted in a total of 40 subjects; however, only 25 were tested before the end of the cold season. In addition to the reduced number of subjects, the study ran about twice as long as is usual with this group. Mr. Boffa, the laboratory director, has submitted the following comment in regard to the difficulty in completing this study: "The reason may well be a reluctance on the part of subjects to submit to clinical investigational procedures due to the adverse material printed in newspapers and other media relating to new drug side effects particularly the Public Senate Hearings conducted for contraceptive medication".

Protocol and Methodology

A total of 25 subjects with head colds and having confirmed nasal congestion on two consecutive days participated in the study. Evaluation of the degree of nasal congestion was made by measuring the relative resistance to a constant flow of air passing through the nasal passageway by a modification of the Butler-Ivy procedure (Blanchard et al E.E.N.T. Monthly 43, 76-82, 1964).

The subjects were assigned coded drugs on a double-blind randomized basis. The randomization was designed so that half the subjects in each dose category received placebo on the first day and active medication on the second day. The reversed sequence occurred with the other subjects. The following table gives the number of subjects receiving each of the drugs.

No. of Subjects	Neo-Synephrine vs. Placebo
10	10 mg
6	15 mg
9	25 mg

Cardiovascular changes attributable to Neo-Synephrine were seen. These consisted of minor but statistically significant increases in systolic blood pressure, a minor increase in diastolic blood presssure at the 10 mg dose only and an increase in pulse rate on all three doses. The latter was an increase and thus opposite to that expected of a drug effect.

N. A. Hulme

bjc
Attachments

cc: Dr. Wessinger
Dr. Luduena
Mr. Stander
Dr. Cox
Dr. Surrey
Mr. Heike
Dr. Gerding
Dr. Rees
File

Table I

COMPARISON OF THE NASAL DECONGESTANT EFFECT OF ORAL NEO-SYNEPHRINE (10 mg, 15 mg, 25 mg) VERSUS PLACEBO IN SUBJECTS WITH COMMON COLD

Objective Measurements (fractional units)

	t_0	t_{15}/t_0	t_{30}/t_0	t_{45}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0	t_{180}/t_0	t_{240}/t_0
Neo-Synephrine 10 mg	13.0	.98	.89	.73	.71	.78	.83	.91	.97
Placebo	12.7	.99	1.02	.98	1.01	1.01	1.00	1.01	1.00
Analysis of Variance (s) (n = 10)	p>0.05 s=0.98	p>0.05 s=0.03	p=0.01 s=0.06	p=0.01 s=0.08	p=0.01 s=0.06	p=0.01 s=0.07	p=0.01 s=0.05	p=0.01 s=0.04	p>0.05 s=0.07
Neo-Synephrine 15 mg	12.1	1.01	.93	.74	.68	.81	.90	.96	1.00
Placebo	12.7	1.00	1.03	1.01	.95	1.03	1.03	1.05	1.02
Analysis of Variance (s) (n = 6)	p>0.05 s=0.95	p>0.05 s=0.03	p=0.05 s=0.05	p=0.05 s=0.13	p=0.05 s=0.18	p=0.01 s=0.09	p=0.05 s=0.08	p=0.05 s=0.06	p>0.05 s=0.07
Neo-Synephrine 25 mg	12.4	.92	.71	.60	.58	.64	.75	.87	.92
Placebo	12.9	.99	.99	1.02	.98	1.02	1.02	1.04	1.03
Analysis of Variance (s) (n = 9)	p>0.05 s=0.55	p>0.05 s=0.07	p=0.01 s=0.12	p=0.01 s=0.13	p=0.01 s=0.09	p=0.01 s=0.09	p=0.01 s=0.09	p=0.01 s=0.09	p=0.01 s=0.07

Table II

COMPARISON OF THE NASAL DECONGESTANT EFFECT OF ORAL NEO-SYNEPHRINE (10 mg, 15 mg, 25 mg) VERSUS PLACEBO IN SUBJECTS WITH COMMON COLD

Subjective Impression Differences

	Median Differences	Analysis of Variance	Standard Deviation	Number of Subjects
Neo-Synephrine 10 mg	-2.2	p>0.05	1.33	10
Placebo	-1.2			
Neo-Synephrine 15 mg	-2.0	p>0.05	2.43	6
Placebo	-2.2			
Neo-Synephrine 25 mg	-4.8	p=0.05	3.40	9
Placebo	-0.9			

Table III

COMPARISON OF THE EFFECT OF ORAL NEO-SYNEPHRINE (10 mg, 15 mg, 25 mg) ON THE PULSE RATE IN SUBJECTS WITH COMMON COLD

(Fractional Units of t_0 Readings)

	t_0	t_{30}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0	t_{180}/t_0	t_{240}/t_0
Neo-Synephrine 10 mg	75.8	1.01	1.01	1.03	1.03	1.01	1.01
Placebo	76.0	.98	.99	1.01	.99	.99	1.00
Analysis of Variance (s) (n = 10)	p>0.05 s=3.68	p>0.05 s=0.05	p>0.05 s=0.04	p>0.05 s=0.03	p=0.05 s=0.03	p>0.05 s=0.06	p>0.05 s=0.05
Neo-Synephrine 15 mg	81.3	1.03	1.07	1.04	1.01	1.03	1.02
Placebo	82.0	1.01	1.00	.97	.96	.95	.98
Analysis of Variance (s) (n = 6)	p>0.05 s=4.16	p>0.05 s=0.04	p=0.05 s=0.04	p=0.05 s=0.03	p>0.05 s=0.08	p>0.05 s=0.07	p>0.05 s=0.04
Neo-Synephrine 25 mg	75.6	1.04	1.07	1.07	1.04	1.05	1.05
Placebo	76.4	.97	1.00	.97	.96	.99	.99
Analysis of Variance (s) (n = 9)	p>0.05 s=2.75	p=0.05 s=0.06	p>0.05 s=0.08	p=0.01 s=0.06	p=0.05 s=0.07	p=0.05 s=0.05	p=0.05 s=0.04

Table IV

COMPARISON OF THE EFFECT OF ORAL NEO-SYNEPHRINE (10 mg, 15 mg, 25 mg) ON THE SYSTOLIC BLOOD PRESSURE IN SUBJECTS WITH COMMON COLD

(Fractional Units of t_0 Readings)

	t_0	t_{30}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0	t_{180}/t_0	t_{240}/t_0
Neo-Synephrine 10 mg	130	1.00	1.01	1.01	1.02	1.02	1.01
Placebo	133	.99	.99	.98	.97	.98	.98
Analysis of Variance (s) (n = 10)	p>0.05 s=3.84	p>0.05 s=0.02	p=0.05 s=0.03	p=0.01 s=0.02	p=0.01 s=0.02	p=0.01 s=0.02	p>0.05 s=0.03
Neo-Synephrine 15 mg	139	.99	1.01	1.01	.99	1.00	1.00
Placebo	140	.97	1.00	.98	.98	.98	.99
Analysis of Variance (s) (n = 6)	p>0.05 s=3.43	p>0.05 s=0.02	p>0.05 s=0.01	p=0.05 s=0.01	p>0.05 s=0.02	p>0.05 s=0.03	p>0.05 s=0.02
Neo-Synephrine 25 mg	133	1.01	1.03	1.03	1.02	1.01	1.02
Placebo	135	1.00	.99	.98	.98	.98	.99
Analysis of Variance (s) (n = 9)	p>0.05 s=1.80	p>0.05 s=0.02	p=0.05 s=0.03	p=0.01 s=0.02	p=0.05 s=0.02	p>0.05 s=0.03	p=0.05 s=0.02

Table V

COMPARISON OF THE EFFECT OF ORAL NEO-SYNEPHRINE (10 mg, 15,mg, 25 mg) ON THE DIASTOLIC BLOOD PRESSURE IN SUBJECTS WITH COMMON COLD

(Fractional Units of t_0 Readings)

	t_0	t_{30}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0	t_{180}/t_0	t_{240}/t_0
Neo-Synephrine 10 mg	73.6	1.00	1.02	1.03	1.03	1.02	.98
Placebo	75.2	.98	.97	.98	.98	.97	.97
Analysis of Variance (s) (n = 10)	p>0.05 s=2.97	p>0.05 s=0.05	p=0.05 s=0.05	p=0.01 s=0.03	p>0.05 s=0.06	p>0.05 s=0.05	p>0.05 s=0.04
Neo-Synephrine 15 mg	77.3	1.01	1.01	1.01	1.00	1.01	1.02
Placebo	77.0	.99	.98	.95	.94	.97	.99
Analysis of Variance (s) (n = 6)	p>0.05 s=6.29	p>0.05 s=0.04	p>0.05 s=0.05	p>0.05 s=0.05	p>0.05 s=0.06	p>0.05 s=0.04	p>0.05 s=0.06
Neo-Synephrine 25 mg	72.9	1.02	1.05	1.07	1.04	1.02	1.04
Placebo	74.6	1.00	1.00	.99	.98	.98	.99
Analysis of Variance (s) (n = 9)	p>0.05 s=1.93	p>0.05 s=0.04	p>0.05 s=0.04	p>0.05 s=0.03	p>0.05 s=0.02	p>0.05 s=0.05	p>0.05 s=0.05

Figure 1

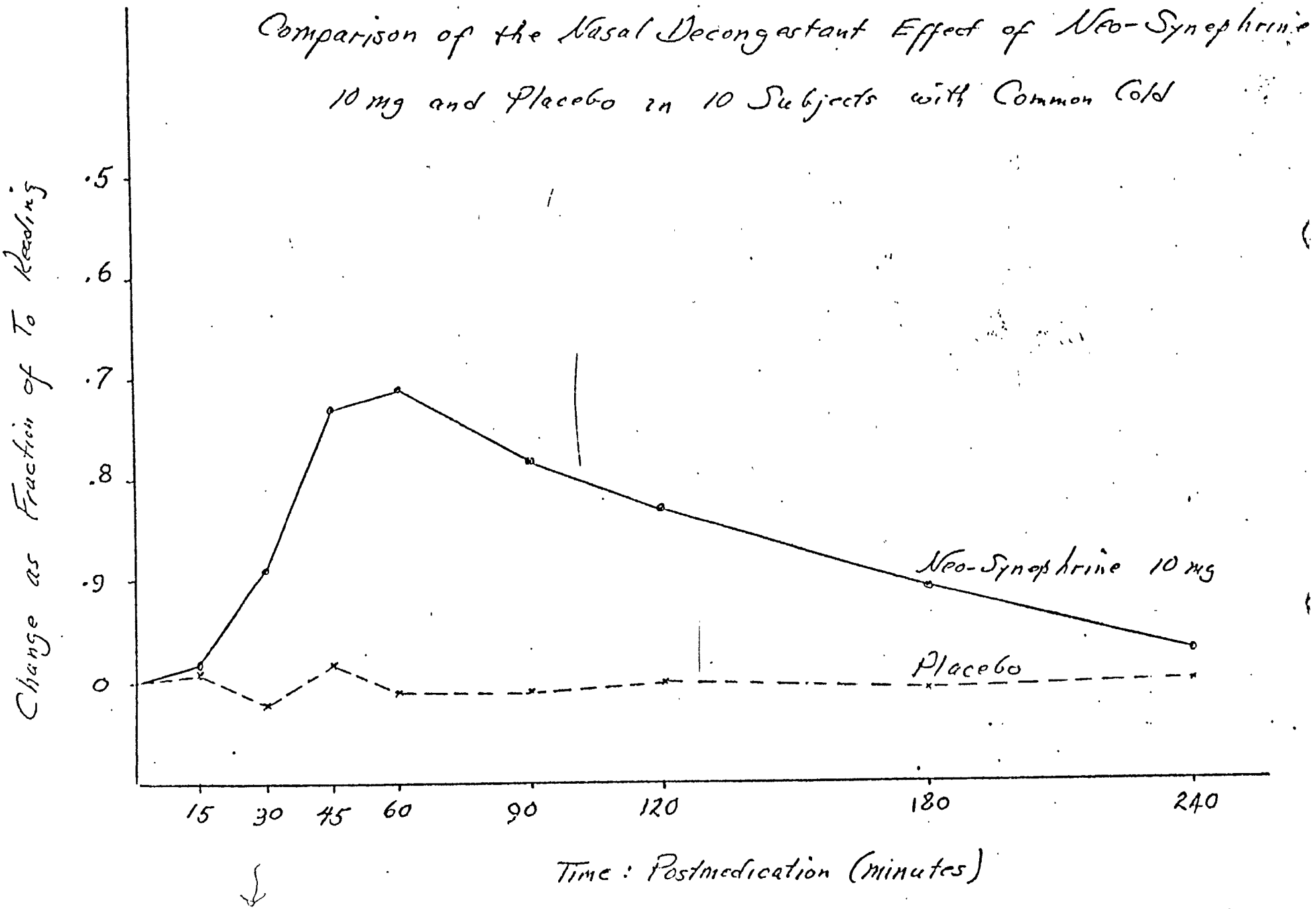

Comparison of the Nasal Decongestant Effect of Neo-Synephrine 10 mg and Placebo in 10 Subjects with Common Cold
Change as Fraction of To Reading
.5
.6
.7
.8
.9
0
Neo-Synephrine 10 mg
Placebo
15
30
45
60
90
120
180
240
Time: Postmedication (minutes)

Figure 2

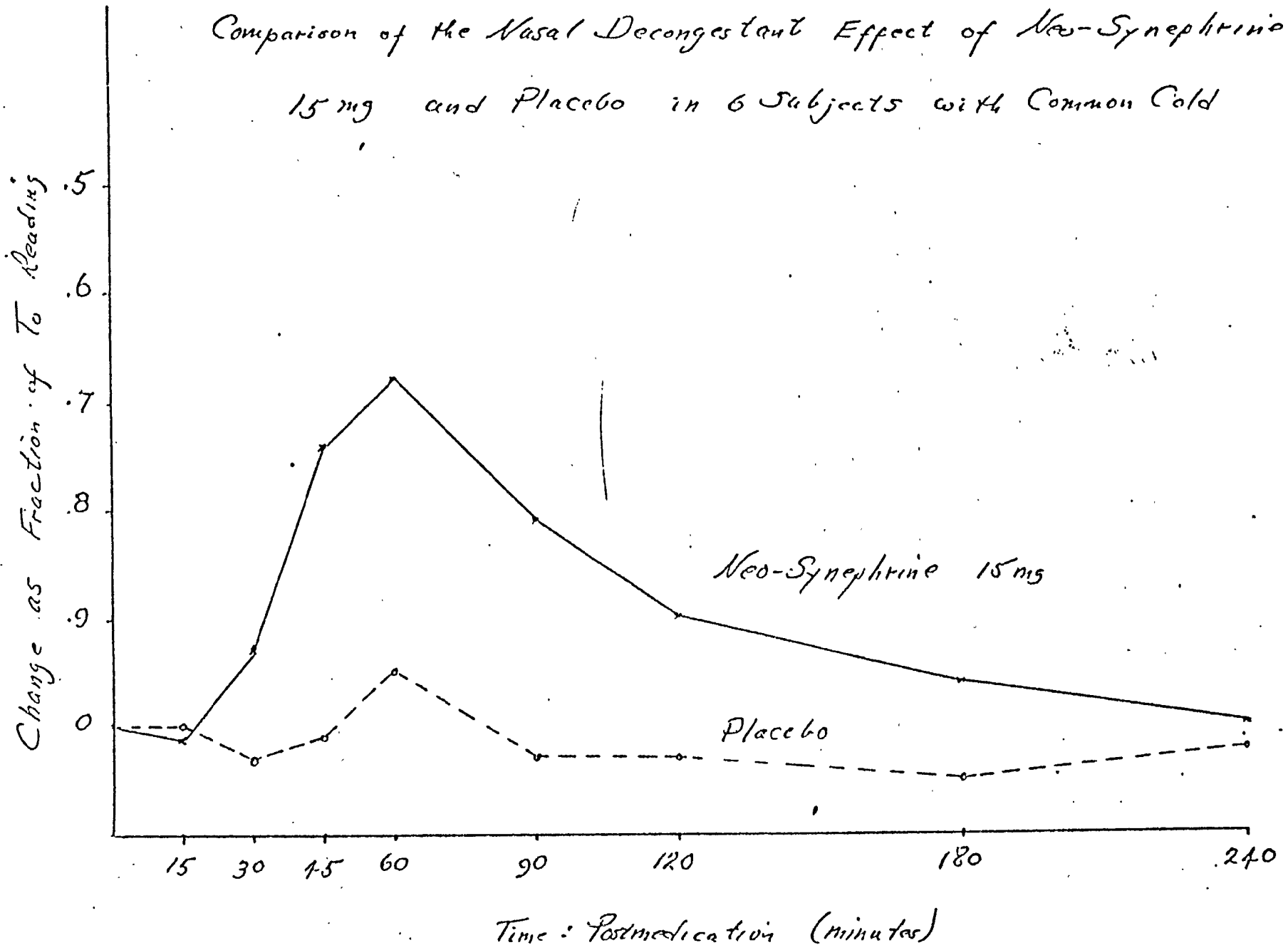
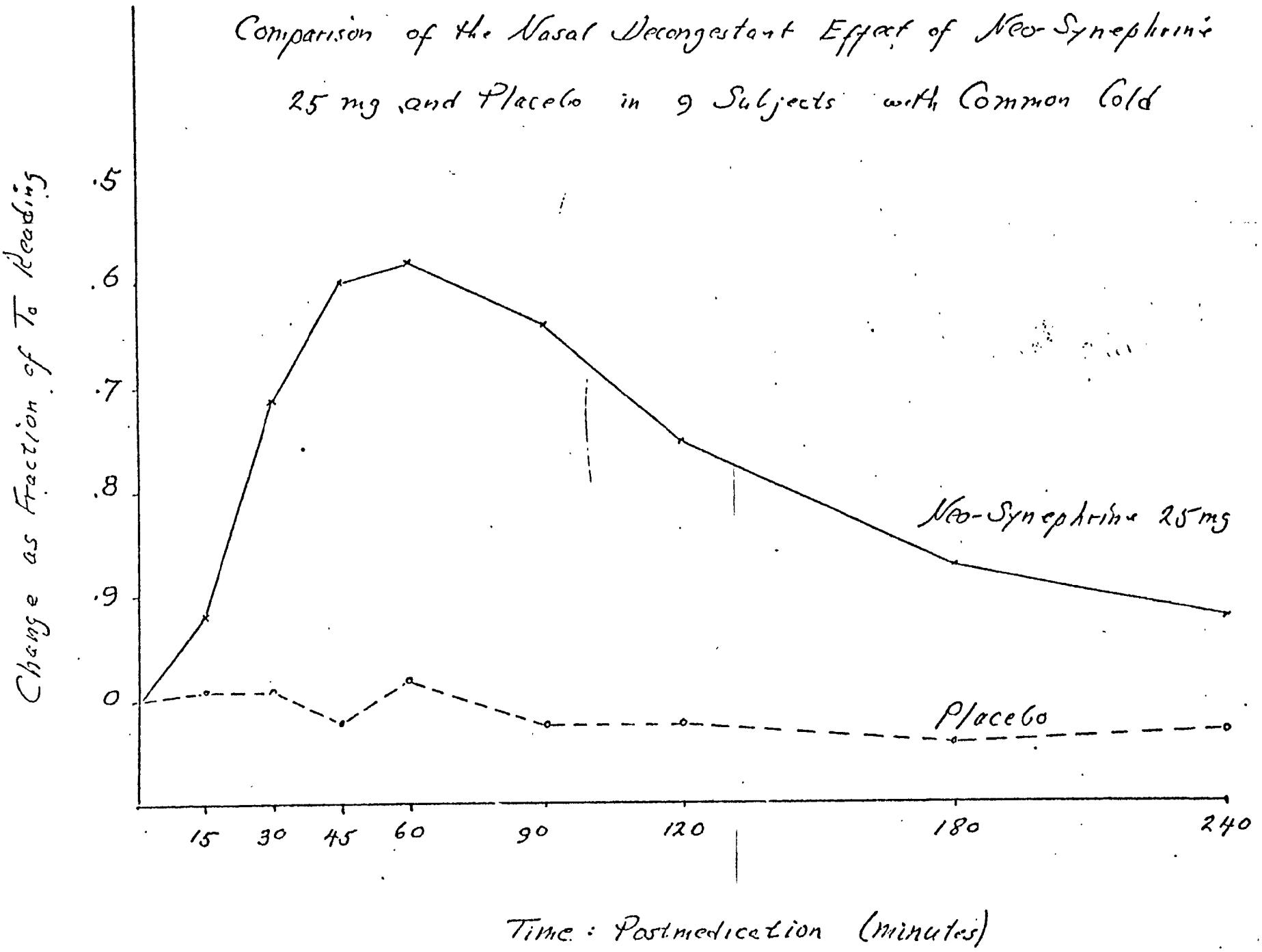

Comparison of the Nasal Decongestant Effect of Neo-Synephrine 15 mg and Placebo in 6 Subjects with Common Cold
Change as Fraction of To Readings
.5
.6
.7
.8
.9
0
Neo-Synephrine 15 mg
Placebo
15
30
45
60
90
120
180
240
Time: Postmedication (minutes)

Figure 3


Comparison of the Nasal Decongestant Effect of Neo-Synephrine 25 mg and Placebo in 9 Subjects with Common Cold
Change as Fraction of T_o Reading
.5
.6
.7
.8
.9
0
Neo-Synephrine 25mg
Placebo
15
30
45
60
90
120
180
240
Time: Postmedication (minutes)

Objective Measurement Means*
Neo-Synephrine (10 mg)

Patient	Treatment	t_0**	t_{15}***	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}	t_{180}	t_{240}
1	Drug	11.7	0.93	0.76	0.47	0.60	0.76	0.69	0.98	1.15
	Placebo	13.7	0.90	0.99	0.97	0.97	1.01	0.96	0.98	0.98
5	Drug	14.1	0.96	0.88	0.66	0.61	0.77	0.81	0.87	0.99
	Placebo	11.5	1.07	1.08	1.03	0.97	1.01	1.00	1.00	0.91
7	Drug	12.1	0.97	0.93	0.75	0.77	0.82	0.97	1.02	0.98
	Placebo	11.7	0.99	1.03	1.01	1.03	1.02	0.99	1.02	0.98
12	Drug	14.3	1.01	0.98	0.80	0.64	0.72	0.80	0.84	0.92
	Placebo	14.7	0.99	0.98	1.01	0.99	1.00	0.99	1.00	1.03
14	Drug	11.9	0.97	0.83	0.75	0.71	0.70	0.80	0.88	0.88
	Placebo	13.7	0.99	1.01	0.99	1.04	0.98	0.99	0.99	1.04
18	Drug	12.0	1.00	0.86	0.80	0.74	0.63	0.77	0.88	0.97
	Placebo	11.4	1.02	1.03	0.98	1.11	1.06	1.03	1.01	0.99
20	Drug	13.2	1.02	0.92	0.76	0.80	0.89	0.85	0.91	0.95
	Placebo	11.8	0.98	1.03	0.98	0.98	0.96	1.03	1.04	0.98
21	Drug	12.7	0.97	0.85	0.66	0.66	0.87	0.93	0.97	0.98
	Placebo	12.4	1.02	1.06	1.06	1.07	1.08	1.07	1.07	1.02
23	Drug	13.3	1.00	1.01	0.80	0.74	0.80	0.89	0.94	0.95
	Placebo	12.6	0.98	1.02	0.98	0.98	0.99	0.97	1.00	1.02
24	Drug	14.5	0.96	0.89	0.79	0.81	0.83	0.84	0.86	0.96
	Placebo	13.7	0.94	1.02	0.96	0.95	0.96	0.97	0.99	1.03

*Each number represents the mean of 5 measurements on both right and left nostrils.

t_0: premedication reading (units) *t_{15}, etc.: Mean as % of t_0

APPENDIX

Objective Measurement Means*
Neo-Synephrine (15 mg)

Patient	Treatment	t_0**	t_{15}***	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}	t_{180}	t_{240}
4	Drug	11.5	1.04	0.84	0.86	0.78	0.90	0.99	1.00	1.00
	Placebo	14.4	0.99	0.99	0.97	0.92	1.03	0.94	0.96	1.00
6	Drug	11.3	1.03	0.96	0.79	0.74	0.77	0.95	0.99	1.01
	Placebo	10.8	1.06	1.01	1.05	0.98	1.12	1.07	1.07	1.04
8	Drug	12.0	1.00	0.96	0.49	0.53	0.77	0.83	0.92	0.99
	Placebo	13.3	1.03	1.06	1.02	1.05	1.04	1.03	1.04	1.05
9	Drug	11.0	1.04	0.88	0.77	0.80	0.95	0.94	0.98	1.06
	Placebo	11.7	0.97	1.08	1.00	0.66	0.99	1.04	1.12	0.93
10	Drug	13.7	0.99	1.00	0.99	0.65	0.68	0.77	0.84	0.88
	Placebo	13.3	1.02	1.00	1.03	1.04	1.01	1.07	1.05	1.07
25	Drug	12.9	0.97	0.95	0.55	0.54	0.79	0.94	1.01	1.08
	Placebo	12.5	0.94	1.03	1.01	1.05	1.03	1.05	1.07	1.05

*Each number represents the mean of 5 measurements on both right and left nostrils.

t_0: premedication reading (units) *t_{15}, etc.: Mean as % of t_0

APPENDIX

Objective Measurement Means*
Neo-Synephrine (25 mg)

Patient	Treatment	t_0**	t_{15}***	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}	t_{180}	t_{240}
2	Drug	11.6	0.77	0.51	0.51	0.52	0.53	0.85	0.96	0.99
	Placebo	12.3	0.98	0.99	1.05	0.98	1.04	1.09	1.08	1.13
3	Drug	15.3	0.72	0.45	0.41	0.39	0.46	0.73	0.82	0.97
	Placebo	16.0	0.97	0.96	0.97	0.94	0.94	0.94	0.97	0.96
11	Drug	14.4	0.99	0.90	0.38	0.42	0.52	0.56	0.78	0.83
	Placebo	16.0	0.92	0.93	0.99	0.96	0.96	0.99	1.02	0.97
13	Drug	11.8	0.94	0.74	0.81	0.71	0.76	0.80	0.90	0.87
	Placebo	13.3	0.99	0.98	1.03	0.94	0.99	1.00	1.01	0.96
15	Drug	11.7	0.94	0.63	0.62	0.64	0.76	0.76	0.83	0.90
	Placebo	11.5	1.00	1.02	0.99	0.91	1.00	0.98	1.03	1.01
16	Drug	10.6	1.01	0.85	0.58	0.65	0.78	0.78	0.85	0.86
	Placebo	11.3	1.02	1.02	1.03	1.01	1.03	1.02	1.09	1.07
17	Drug	12.5	0.95	0.73	0.63	0.58	0.55	0.58	0.69	0.81
	Placebo	11.6	1.06	1.05	1.07	1.10	1.10	1.09	1.11	1.11
19	Drug	11.6	0.97	0.99	0.99	0.54	0.60	0.73	0.99	1.01
	Placebo	11.9	1.01	1.00	1.02	0.95	1.03	0.99	0.99	1.05
22	Drug	11.9	0.96	0.63	0.50	0.78	0.82	0.96	1.03	1.04
	Placebo	12.5	1.00	1.00	1.02	1.03	1.07	1.05	1.07	1.06

*Each number represents the mean of 5 measurements on both right and left nostrils.

t_0: premedication reading (units) *t_{15}, etc.: Mean as % of t_0

REFERENCE 4

McLaurin, J. W., W. F. Shipman, and R. Rosedale, Jr., "A Double Blind Comparison Study of the Effectiveness of Four Sympathomimetic Drugs: Objective and Subjective," *Laryngoscope*, 71:54-67, 1961.

REFERENCE 5

INTER-OFFICE MEMORANDUM

STERLING-WINTHROP RESEARCH INSTITUTE

RENSSELAER, NEW YORK

May 13, 1969

Ref #20

To: Dr. Blackmore

From: N. A. Hulme

Re: Oral Neo-Synephrine - Huntingdon Research Center Study No. 1

The study carried out by Huntingdon Research Center on the activity of orally administered Neo-Synephrine was recently completed. The results have been evaluated and are presented below. This study is the second such study carried out for the purpose of expanding the clinical testing capacity available to us for evaluating orally active decongestants and for the purpose of confirming the earlier data obtained by the Elizabeth Biochemical Labs.

Protocol and Methodology

The protocol and methodology was identical to that followed in the Cintest Labs study. Details of this are fully described in the report of Hulme to Blackmore of April 10, 1969. The Butler-Ivy airflow instrument utilized in the study was similar to that used by the Cintest group. Data analysis was provided by Mr. Stander.

Results

As in the Cintest Labs study the mean of the air resistance readings for each subject was calculated as the percent (fractional units x 100) change from the last premedication reading (see appendix). The combined data was then analyzed for significance between the placebo and medication groups at each of the time intervals. The level of significance for each of the drugs at the indicated time interval are given in Table I. The data plotted as a graph for the phenylpropanolamine:placebo pair only is given in Figure 1. As will be noted in Table I periods of significant differences occurred at 45 and 60 minutes following medication with the 50 mg dose of phenylpropanolamine but did not occur with Neo-Synephrine at either of the two doses (10 mg or 25 mg) tested.

A comparison of the differences in the subjective measurements were not made because of missing data at certain critical time periods and failure to obtain positive objective data for correlative purposes.

Discussion

The failure to find statistically valid differences between placebo medication and Neo-Synephrine medication at the 10 and 25 mg levels but a statistical differences between placebo and 50 mg

phenylpropanolaime is somewhat surprising in view of the earlier data obtained by Elizabeth Biochemical Labs and recently confirmed by the Cintest study. The reasons for this could be several. An examination of the case reports indicates that what may be one of the causes is the fact that a series of several technicians were used in operating the instrument. For a study limited to 48 subject it is likely that too few, if any, of the number were able to develop a sufficiently high degree of competence or skill to optimally measure air resistance. An additional variable added to this was the use of a different technician to take airflow readings for each half of the two crossover days for 14 of the subjects. (It was requested that the latter practice be stopped at the time the first group of case reports were examined and that the use of the instrument be limited to one or two well-trained personnel.)

Another factor apparent from the data may be related in a general way to the competence of the pupulation of subjects taking part in this particular study to respond to decongestant action. It will be noted that the maximum effect produced by 50 mg phenylpropanolamine was 4 units or a 20% decrease in airflow resistance over premedication readings. This was in contrast to a 10 unit or 45% decrease observed in the Cintest study and 7 units or 48% change seen for the same dose of phenylpropanolamine by Elizabeth Biochemical Labs. The maximum decrease observed for either of the Neo-Synephrine doses in the study was approximately 15%. These small changes were apparently not sufficiently large to permit statistically significant differences to appear with Neo-Synephrine medication and at only two time periods (45 to 60 minutes) with phenylpropanolamine.

Further examination of the statistical data reveals a greater spread in values obtained in this study than in previous studies which in turn are reflected in larger standard deviation values at each of the time periods. A comparison of the s values (standard deviation) obtained for the three studies is provided in Table II for phenylpropanolamine 50 mg and for Neo-Synephrine at several dosages. (For purposes of comparison s values are compared as the square of their ratios. For instance, where s = 28 one would need to double the number of subjects to have the same significance if s = 20). It will be noted that the s values for the two time periods of significance at the 50 mg phenylpropanolamine dose are lower than the same periods for the Neo-Synephrine doses. This greater precision of measurement combined with the possibly greater potency of the 50 mg dose of phenylpropanolamine in comparison to the two Neo-Synephrine doses could well add to the failure of the latter two to fall above the threshold level of significance.

The failure to find a significant difference between placebo and Neo-Synephrine is not to be taken in a negative sense, that is, it does not mean that a difference does not exist between the two medications,

but only that under the conditions and restraints operating at the time this particular experiment was conducted that a positive correlation was not demonstrated.

N. A. Hulme.

bjc
Attachments

cc: Dr. Wessinger
Dr. Luduena
Mr. Stander
Dr. Cox
Dr. Surrey
Mr. Heike
Dr. Gerding
Dr. Rees
Dr. Giambalvo
File

Table 1

COMPARISON OF THE NASAL DECONGESTANT EFFECT OF ORAL PHENYLPROPANOLAMINE (50 mg) AND NEO-SYNEPHRINE (10 mg, and 25 mg) VERSUS PLACEBO IN SUBJECTS WITH "COMMON COLD"

Objective Measurements (fractional units x 100)

	t_0 (units)	t_{15}/t_0	t_{30}/t_0	t_{45}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0	t_{180}/t_0	t_{240}/t_0
Neo-Synephrine (10 mg)	24.6	94	97	100	95	90	104	86	93
Placebo	23.8	93	95	95	94	91	97	102	138
Analysis of Variance Comparison between treatments (n = 16)	p>0.1 s=7.7	p>0.1 s=12	p>0.1 s=18	p>0.1 s=18	p>0.1 s=28	p>0.1 s=22	p>0.1 s=58	p>0.1 s=79	p>0.1 s=166
Neo-Synephrine (25 mg)	25.5	101	111	102	104	96	92	98	94
Placebo	22.1	97	110	108	118	103	104	100	81
Analysis of Variance Comparison between treatments (n = 16)	p>0.1 s=10.0	p>0.1 s=22	p>0.1 s=29	p>0.1 s=32	p>0.1 s=38	p>0.1 s=44	p>0.1 s=45	p>0.1 s=55	p>0.1 s=44
Phenylpropanolamine (50 mg)	22.3	101	95	87	87	81	81	83	80
Placebo	24.3	111	106	106	108	97	91	90	87
Analysis of Variance Comparison between treatments (n = 16)	p>0.1 s=6.5	p>0.1 s=27	p>0.1 s=20	p=0.01 s=16	p=0.05 s=25	p>0.1 s=37	p>0.1 s=36	p>0.1 s=38	p>0.1 s=38

Fig. 1

Comparison of the Nasal Decongestant Effect of Oral Phenylpropanolamine 50mg and Placebo in 16 Subjects with "Common Cold"

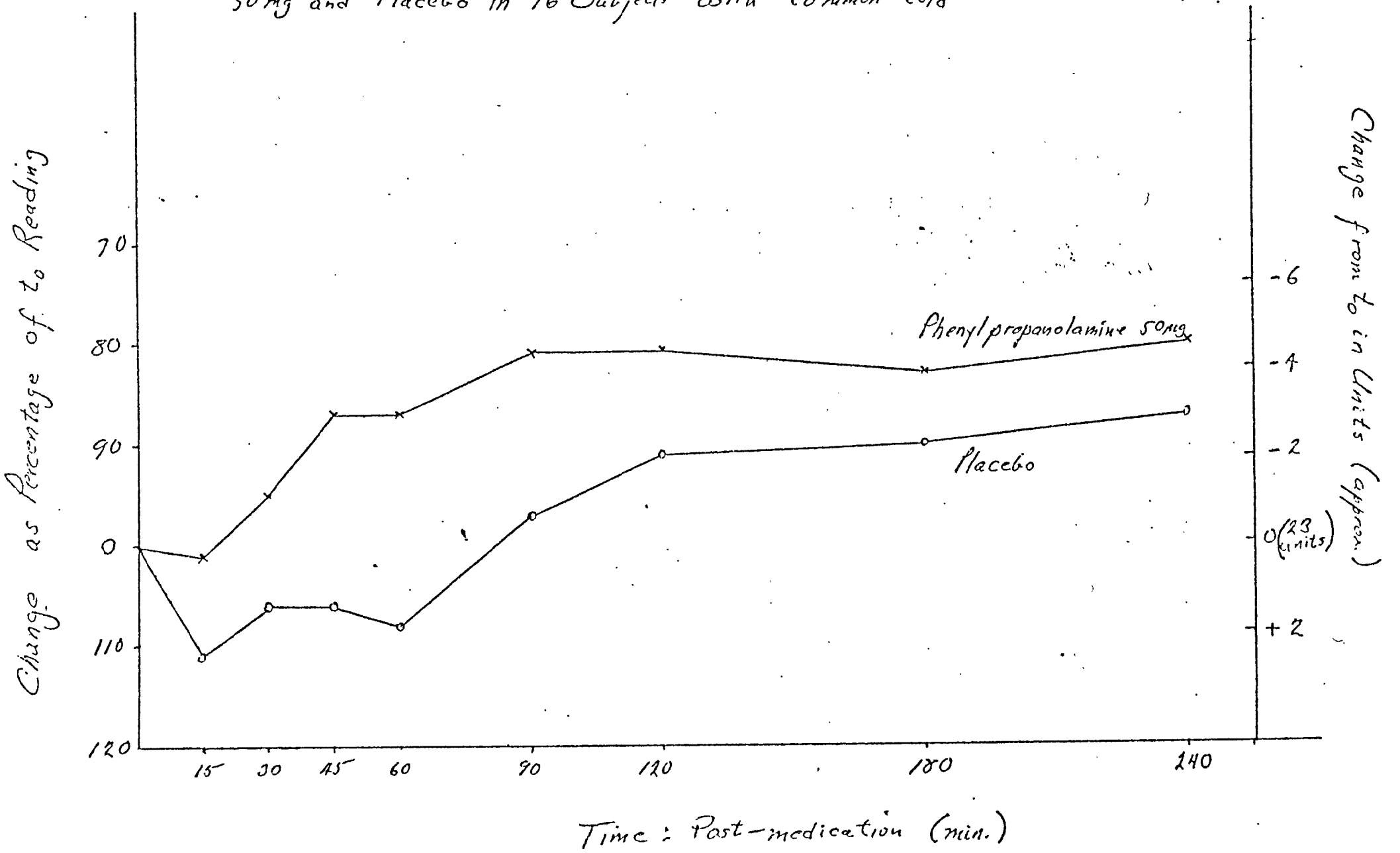


Table II

Comparison of Standard Deviation Values (s) for Decongestant Studies nducted at Elizabeth Biochemical Labs, Cintest Labs and Huntingdon Research Center

	Time 0	15	30	45	60	90	120	180	240
50 mg phenylpropanolamine									
Eliz. Biochem. Labs	1.3	0.7	0.9	0.9	1.5	1.8	2.1	2.6	2.3
Cintest	4.1	12	13	18	20	17	18	23	45
Huntingdon Res. Center	6.5	27	20	16	25	37	36	38	38
10 mg Neo-Synephrine									
Cintest	7.3	12	14	16	21	21	23	27	42
Huntingdon Res. Center	7.7	12	18	18	28	22	58	79	166
25 mg Neo-Synephrine									
Cintest	5.4	14	22	23	21	22	22	22	30
Huntingdon Res. Center	10	22	29	32	38	44	45	55	44
15 mg Neo-Synephrine									
Eliz. Biochem. Labs	0.8	0.3	1.0	1.7	2.1	1.5	1.5	1.4	2.3

Objective Measurement Means*
Neo-Synephrine (10 mg)

Patient	Treatment	t_0**	t_{15}***	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}	t_{180}	t_{240}
1	Drug	21.8	0.88	0.86	0.76	0.79	0.75	0.75	0.80	0.80
	Placebo	16.6	0.90	1.05	0.98	0.87	0.93	0.84	0.68	0.63
3	Drug	53.6	0.81	0.77	0.78	0.72	0.49	0.46	0.49	0.61
	Placebo	43.5	1.04	0.94	0.83	0.69	0.88	0.84	0.71	0.70
5	Drug	6.7	1.27	1.32	1.64	1.41	1.60	3.37	1.13	2.03
	Placebo	13.6	1.02	0.97	1.06	1.07	1.52	1.61	1.64	0.56
8	Drug	15.4	0.86	0.81	1.10	1.09	1.02	0.91	1.09	0.96
	Placebo	24.3	0.99	1.24	1.20	0.85	0.63	0.51	0.57	1.06
10	Drug	22.7	0.94	0.89	0.90	0.80	0.73	0.68	0.77	0.84
	Placebo	23.0	1.01	0.93	0.86	0.86	0.77	0.81	0.82	0.79
13	Drug	29.4	0.85	0.89	1.09	0.99	0.70	0.95	0.76	0.84
	Placebo	34.1	1.08	1.21	1.10	0.94	0.48	0.25	0.42	0.56
17	Drug	30.1	0.72	0.70	0.74	0.68	0.67	0.75	0.71	0.82
	Placebo	30.9	0.88	0.76	0.84	1.16	0.64	0.60	0.37	0.92
23	Drug	22.7	1.07	1.34	1.28	1.28	1.10	1.18	1.16	1.27
	Placebo	22.5	1.13	0.91	0.93	0.97	1.27	0.95	1.15	1.06
26	Drug	45.5	0.95	0.94	0.88	1.00	1.02	0.91	0.91	1.12
	Placebo	10.4	0.96	0.93	1.11	1.95	1.47	2.92	5.07	10.2
31	Drug	15.5	0.98	0.96	0.84	0.82	0.77	0.81	0.68	0.72
	Placebo	23.5	0.75	0.63	0.87	0.88	0.70	0.76	0.73	0.74
34	Drug	26.3	0.87	1.10	1.16	1.01	0.86	0.89	0.72	1.17
	Placebo	27.9	0.96	0.94	0.90	0.77	1.07	0.98	0.70	0.90
40	Drug	12.1	0.99	1.01	1.06	1.06	1.03	1.05	1.15	1.09
	Placebo	19.7	0.73	0.75	0.73	0.72	0.87	0.90	0.65	1.29
41	Drug	16.9	0.89	0.80	0.86	0.71	1.10	1.30	0.77	0.84
	Placebo	19.1	0.71	0.64	0.67	0.73	0.61	0.74	0.39	0.43
44	Drug	14.7	0.90	1.11	0.86	0.59	0.77	0.54	0.56	0.72
	Placebo	6.5	0.92	1.39	1.32	1.22	1.43	1.73	1.06	0.92
46	Drug	38.7	1.05	1.09	1.14	1.24	0.72	0.97	1.07	0.98
	Placebo	35.2	0.81	0.96	0.93	0.63	0.61	0.38	0.59	0.74
48	Drug	21.7	0.98	0.85	0.93	1.00	1.00	1.04	0.94	0.92
	Placebo	30.8	0.99	0.97	0.80	0.75	0.70	0.62	0.70	0.58

*Each number represents the mean of 5 measurements on both right and left nostrils.

t_0: premedication reading (units) *t_{15}, etc: mean as % of t_0

Objective Measurement Means*
Neo-Synephrine (25 mg)

Patient	Treatment	t_0**	t_{15}***	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}	t_{180}	t_{240}
2	Drug	47.1	0.85	0.92	0.63	0.64	0.25	0.42	0.23	0.29
	Placebo	13.7	1.23	1.16	1.17	1.25	1.60	1.65	1.97	0.86
4	Drug	14.1	1.00	1.03	1.00	1.04	1.01	1.03	1.71	1.47
	Placebo	22.6	0.84	0.81	0.70	0.74	0.73	0.70	0.66	0.64
9	Drug	22.8	1.18	0.98	1.03	1.06	1.04	1.06	0.82	0.84
	Placebo	13.9	1.27	1.37	1.42	1.40	1.33	1.64	1.62	1.53
12	Drug	17.8	0.94	1.00	0.96	0.95	1.16	0.94	0.93	0.90
	Placebo	15.3	1.16	1.03	1.16	1.12	0.90	1.01	0.85	0.85
19	Drug	29.4	1.13	1.39	0.90	0.96	1.29	1.23	0.94	0.99
	Placebo	41.5	0.66	0.34	0.56	0.41	0.51	0.72	0.71	0.36
20	Drug	41.5	0.80	0.80	1.06	1.28	0.38	0.27	0.23	0.22
	Placebo	11.6	0.94	0.98	1.41	1.28	1.58	1.46	1.27	1.41
21	Drug	23.1	1.02	1.00	1.07	1.05	1.09	1.18	1.16	1.28
	Placebo	19.2	1.05	1.13	2.10	2.67	1.77	1.85	1.17	0.45
24	Drug	19.1	0.95	1.21	0.92	1.07	0.37	0.77	0.77	0.72
	Placebo	9.1	0.79	0.82	1.11	0.84	1.08	1.03	0.75	0.84
27	Drug	15.4	0.98	1.14	1.09	1.00	1.48	1.81	1.85	1.54
	Placebo	29.0	1.36	1.45	1.19	1.49	1.02	1.15	0.88	0.67
28	Drug	31.5	0.90	1.17	1.19	1.13	1.15	0.39	0.57	0.70
	Placebo	27.9	0.77	0.73	0.68	1.02	1.06	0.90	1.09	1.00
29	Drug	12.4	1.10	1.04	0.92	1.01	1.16	0.59	1.05	0.75
	Placebo	11.1	0.74	0.90	1.07	1.33	1.24	0.97	1.31	0.90
35	Drug	12.9	1.14	1.24	0.92	1.20	1.41	1.20	1.16	1.40
	Placebo	8.8	0.73	0.77	0.49	0.60	0.46	0.33	0.20	0.51
36	Drug	28.0	1.19	1.37	1.55	1.49	1.07	0.78	0.56	1.16
	Placebo	25.5	1.44	1.65	1.30	1.68	0.81	0.81	1.18	0.51
37	Drug	46.6	1.41	1.42	1.43	1.39	1.43	1.25	1.46	1.08
	Placebo	38.4	1.21	1.23	1.20	1.19	1.20	1.08	1.22	1.12
38	Drug	15.8	1.02	1.23	0.95	0.75	0.93	1.43	1.20	1.07
	Placebo	14.0	0.50	0.55	0.42	0.87	0.94	0.82	0.75	0.88
39	Drug	30.3	0.50	0.89	0.64	0.64	0.42	0.39	1.04	0.62
	Placebo	52.0	0.82	1.08	1.24	1.01	0.44	0.52	0.44	0.38

*Each number represents the mean of 5 measurements on both right and left nostrils.

t_0: premedication reading (units) *t_{15}, etc.: mean as % of t_0

Objective Measurement Means*
Phenylpropanolamine (50 mg)

Patient	Treatment	t_0**	t_{15}***	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}	t_{180}	t_{240}
6	Drug	14.1	0.99	0.92	0.82	0.86	0.77	0.78	0.63	1.02
	Placebo	12.0	1.08	1.11	0.96	1.27	1.32	1.11	1.56	0.92
7	Drug	16.0	1.21	1.02	0.91	0.97	0.62	0.54	0.64	0.76
	Placebo	19.4	1.36	1.34	1.16	1.58	1.42	1.14	1.12	1.22
11	Drug	11.9	1.34	0.80	0.62	0.60	0.58	0.52	0.43	0.64
	Placebo	16.2	0.96	0.84	0.68	0.48	0.50	0.46	0.51	0.49
14	Drug	27.1	0.92	1.04	0.79	0.81	1.25	0.95	1.01	0.84
	Placebo	25.8	1.51	1.08	1.36	1.15	0.94	1.15	1.31	1.41
15	Drug	28.9	0.69	0.86	0.68	0.63	0.64	0.64	0.67	0.65
	Placebo	34.5	1.20	1.12	1.20	1.37	1.18	1.16	1.14	1.20
16	Drug	16.0	1.14	1.06	1.05	1.16	1.14	1.02	1.06	0.90
	Placebo	20.5	1.02	1.06	1.20	1.15	1.20	1.05	0.94	1.00
18	Drug	15.8	0.93	1.00	0.90	0.78	0.63	0.62	0.69	0.63
	Placebo	20.3	1.41	1.01	1.11	1.20	0.70	0.65	0.55	0.45
22	Drug	18.2	1.13	1.03	1.04	1.16	0.98	0.65	0.65	0.57
	Placebo	17.2	0.76	1.02	1.01	1.31	0.74	1.20	0.64	0.50
25	Drug	56.8	0.88	0.60	0.31	0.25	0.20	0.36	0.41	0.46
	Placebo	43.5	0.96	0.80	0.54	0.78	1.07	0.94	1.04	0.70
30	Drug	23.0	1.21	0.95	1.11	1.31	1.10	1.24	1.36	1.03
	Placebo	43.8	1.03	1.18	1.26	1.14	0.98	0.41	0.52	0.79
32	Drug	23.5	0.87	0.94	1.23	0.88	1.44	1.62	1.02	0.83
	Placebo	32.3	0.90	0.75	0.95	0.76	0.70	0.84	0.60	0.47
33	Drug	29.2	0.83	1.07	1.17	0.87	0.53	0.61	0.67	0.37
	Placebo	14.7	1.22	1.36	1.62	1.55	1.72	1.43	1.46	1.82
42	Drug	18.4	1.00	0.99	0.98	0.99	0.88	0.90	0.94	0.94
	Placebo	18.3	0.97	0.97	0.97	0.98	0.36	0.32	0.33	0.30
43	Drug	15.9	0.72	0.72	0.83	0.77	0.78	0.70	0.90	0.73
	Placebo	22.8	1.50	1.22	0.96	0.90	0.81	0.91	0.69	0.54
45	Drug	14.6	1.28	1.40	0.86	1.45	0.78	1.31	1.56	1.74
	Placebo	29.2	0.75	0.79	0.85	0.98	0.83	0.98	0.86	1.06
47	Drug	27.3	0.95	0.72	0.57	0.49	0.58	0.56	0.63	0.61
	Placebo	18.7	1.12	1.35	1.08	0.73	1.04	0.75	1.05	1.06

*Each number represents the mean of 5 measurements on both right and left nostrils.

t_0: premedication readings (units) *t_{15}, etc.: mean as % of t_0

REFERENCE 6

INTER-OFFICE MEMORANDUM

STERLING-WINTHROP RESEARCH INSTITUTE

RENSSELAER, NEW YORK

June 26, 1969

To: Dr. Blackmore

From: N. A. Hulme

Re: Oral Neo-Synephrine - Huntingdon Research Center Study No. 2

This study was designed for the purpose of accumulating additional data on subjects having head colds who were administered 10 and 20 mg dosages of Neo-Synephrine and on whom observations could be made for objective and subjective changes in nasal congestion. In addition, concomitant measurements of pulse and blood pressure were carried out in order to detect possible cardiovascular changes which might be produced at these dose levels of the drug.

Protocol and Methodology

A total of 50 subjects with head colds and having confirmed nasal congestion on two consecutive days participated in the study. Evaluation of the degree of nasal congestion was made by measuring the relative resistance to a flow of air passing through the nasal passageway at a constant rate by means of a modification of the Butler-Ivy procedure (Blanchard et al E.E.N.T. Monthly 43, 76-82, 1964).

The subjects were assigned coded drugs on a double-blind randomized basis and objective airflow measurements were made in a manner similar to that previously described for other studies in this series (e.g., Hulme to Blackmore 6-2-69). In this study 25 subjects received 10 mg Neo-Synephrine and 25 subjects 20 mg Neo-Synephrine with placebo on the alternate days.

Subjective impressions of changes in nasal congestion were obtained using the previously described techniques.

Pulse and sitting blood pressure readings were obtained on each subject at 30, 15 and 0 minutes before medication and at 30, 60, 90, 120, 180 and 240 minutes following medication. The readings within each medicationstime group were combined and the arithmetic means employed for further calculations and analysis. This provided comparisons between active medication and placebo for diastolic pressure, systolic pressure and pulse rate.

Results

The mean of the air resistance readings for each subject was analyzed for significance between the placebo and medication groups

at each of the time intervals (see appendix). The levels of significance for each of the drugs at the indicated time interval along with the percent change (fractional units x 100) from the last premedication reading are given in Table I. The data plotted as graphs for each dosage:placebo pair are given in Figures 1 and 2.

The objective readings show a significant difference occurring between the (20) mg Neo-Synephrine:placebo pairs at the 45 minute time interval only. Differences between 10 mg Neo-Synephrine and placebo of statistical significance were not observed at any point although less resistance to airflow was recorded at all time intervals for subjects receiving active drug. — 20 mg only

Analysis of the subjective feelings of change in degree of congestion were not attempted in view of the lack of statistically valid differences in objective readings with the 10 mg dose and only the single point of significance at the 20 mg dose.

Analysis of the pulse rate data indicated that at the 90 minute reading a significant difference occured between placebo and the 10 mg dose of Neo-Synephrine (Table II). No other significant differences occurred at other time periods at the 10 mg dose or with subjects on the 20 mg dose. The one difference observed was of the order of two beats per minute and is not considered to be clinically important.

The systolic blood pressure data showed a single point of statistical difference between placebo and the 10 mg dose of Neo-Synephrine occurring at the 180 minute readings. No differences were seen between the placebo and 20 mg Neo-Synephrine readings (Table III). The single reading observed at the 10 mg dose was of the order of a three mm decrease and was not considered to be clinically meaningful.

Analysis of the diastolic pressure readings indicated a single point of statistical difference occurring at the 240 minute interval in subjects receiving the 20 mg dose of Neo-Synephrine (Table IV). The difference amounted to about eight mm decrease and is not considered to be clinically important. No significant changes in diastolic blood pressure were seen in subjects receiving the 10 mg dose of Neo-Synpehrine.

Discussion

Failure to observe major differences in resistance to nasal airflow in subjects medicated with placebo and Neo-Synephrine appears to follow the pattern seen in the first Huntingdon study (Hulme to Blackmore 5-13-69). One of the primary reasons may again

be the use of a series of several different technicians to operate the instrument rather than to limit the number to one or two competently trained individuals. This point along with several other possible causes for lack of greater differences between Neo-Synephrine and placebo were discussed in the report on the earlier study referred to above.

The pulse and blood changes observed appear to have been isolated points of minimal difference and are not considered to be clinically important.

No side effects were reported by any subject receiving either the placebo or Neo-Synephrine 10 or 20 mg capsules.

N. A. Hulme

bjc
Attachments

cc: Dr. Wessinger
Dr. Luduena
Mr. Stander
Dr. Cox
Dr. Surrey
Mr. Heike
Dr. Gerding
Dr. Rees
Dr. Giambalvo
File

Table I

COMPARISON OF THE NASAL DECONGESTANT EFFECT OF ORAL NEO-SYNEPHRINE 10 AND 20 MG VERSUS PLACEBO IN SUBJECTS WITH COMMON COLD

Objective Measurements (fractional units x 100)

	t_0	t_{15}/t_0	t_{30}/t_0	t_{45}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0	t_{180}/t_0	t_{240}/t_0
Neo-Synephrine 10 mg	26.8	1.04	1.01	1.00	.93	.94	.90	.86	.88
Placebo	28.7	1.00	1.00	.93	.89	.93	.82	.78	.81
Analysis of Variance (s) (n = 25)	p>0.05 s=5.64	p>0.05 s=1.20	p>0.05 s=2.03	p>0.05 s=1.65	p>0.05 s=2.34	p>0.05 s=2.37	p>0.05 s=2.09	p>0.05 s=1.79	p>0.05 s=3.10
Neo-Synephrine 20 mg	24.1	1.12	1.01	1.03	1.00	.93	.92	.92	.91
Placebo	24.6	1.08	.95	.88	.90	.95	.92	.80	.87
Analysis of Variance (s) (n = 24)	p>0.05 s=5.27	p>0.05 s=1.90	p>0.05 s=1.87	p=0.05 s=1.99	p>0.05 s=2.58	p>0.05 s=3.29	p>0.05 s=2.75	p>0.05 s=3.51	p>0.05 s=3.25

T II

COMPARISON OF THE EFFECT OF ORAL NEO-SYNEPHRINE 10 AND 20 MG VERSUS PLACEBO ON THE PULSE RATE IN SUBJECTS WITH COMMON COLD

	t_0	t_{30}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0	t_{180}/t_0	t_{240}/t_0
Neo-Synephrine 10 mg	76.2	.98	.95	.97	.98	1.05	1.03
Placebo	81.0	1.00	.99	1.04	1.08	1.06	1.07
Analysis of Variance (s) (n = 25)	p>0.05 s=8.67	p>0.05 s=0.137	p>0.05 s=0.110	p=0.05 s=0.109	p>0.05 s=0.118	p>0.05 s=0.164	p>0.05 s=0.187
Neo-Synephrine 20 mg	79.8	.98	.99	.99	1.01	1.05	1.03
Placebo	79.4	1.02	.99	1.03	1.04	1.00	1.03
Analysis of Variance (s) (n = 24)	p>0.05 s=8.11	p>0.05 s=0.068	p>0.05 s=0.109	p>0.05 s=0.130	p>0.05 s=0.134	p>0.05 s=0.117	p>0.05 s=0.139

Table III

COMPARISON OF THE EFFECT OF ORAL NEO-SYNEPHRINE 10 AND 20 MG VERSUS PLACEBO ON THE SYSTOLIC BLOOD PRESSURE IN SUBJECTS WITH COMMON COLD

	t_0	t_{30}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0	t_{180}/t_0	t_{240}/t_0
Neo-Synephrine 10 mg	113	.99	.99	1.00	1.00	.98	.98
Placebo	110	1.00	1.01	1.01	1.01	1.02	1.00
Analysis of Variance (s) (n = 25)	p>0.05 s=6.77	p>0.05 s=0.062	p>0.05 s=0.072	p>0.05 s=0.055	p>0.05 s=0.074	p=0.05 s=0.066	p>0.05 s=0.049
Neo-Synephrine 20 mg	115	1.00	.99	.99	.99	1.00	.98
Placebo	117	.99	.97	.99	.99	1.00	.99
Analysis of Variance (s) (n = 24)	p>0.05 s=5.70	p>0.05 s=0.051	p>0.05 s=0.052	p>0.05 s=0.054	p>0.05 s=0.083	p>0.05 s=0.064	p>0.05 s=0.057

Table IV

COMPARISON OF THE EFFECT OF ORAL NEO-SYNEPHRINE 10 AND 20 MG VERSUS PLACEBO ON THE DIASTOLIC BLOOD PRESSURE IN SUBJECTS WITH COMMON COLD

	t_0	t_{30}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0	t_{180}/t_0	t_{240}/t_0
Neo-Synephrine 10 mg	70.3	1.01	.99	1.01	.98	.99	1.00
Placebo	71.6	.99	.98	.99	.98	.96	.97
Analysis of Variance (s) (n = 25)	p>0.05 s=4.66	p>0.05 s=0.086	p>0.05 s=0.076	p>0.05 s=0.080	p>0.05 s=0.136	p>0.05 s=0.092	p>0.05 s=0.11
Neo-Synephrine 20 mg	73.4	1.00	1.00	1.00	.99	.99	.99
Placebo	73.1	1.00	1.01	.98	1.00	1.02	1.06
Analysis of Variance (s) (n = 24)	p>0.05 s=6.40	p>0.05 s=0.073	p>0.05 s=0.085	p>0.05 s=0.075	p>0.05 s=0.090	p>0.05 s=0.092	p=0.05 s=0.092

Figure 1

Comparison of the Nasal Decongestant Effect of Oral Neo-Synephrine 10mg and Placebo in 25 Subjects with "Common Cold"

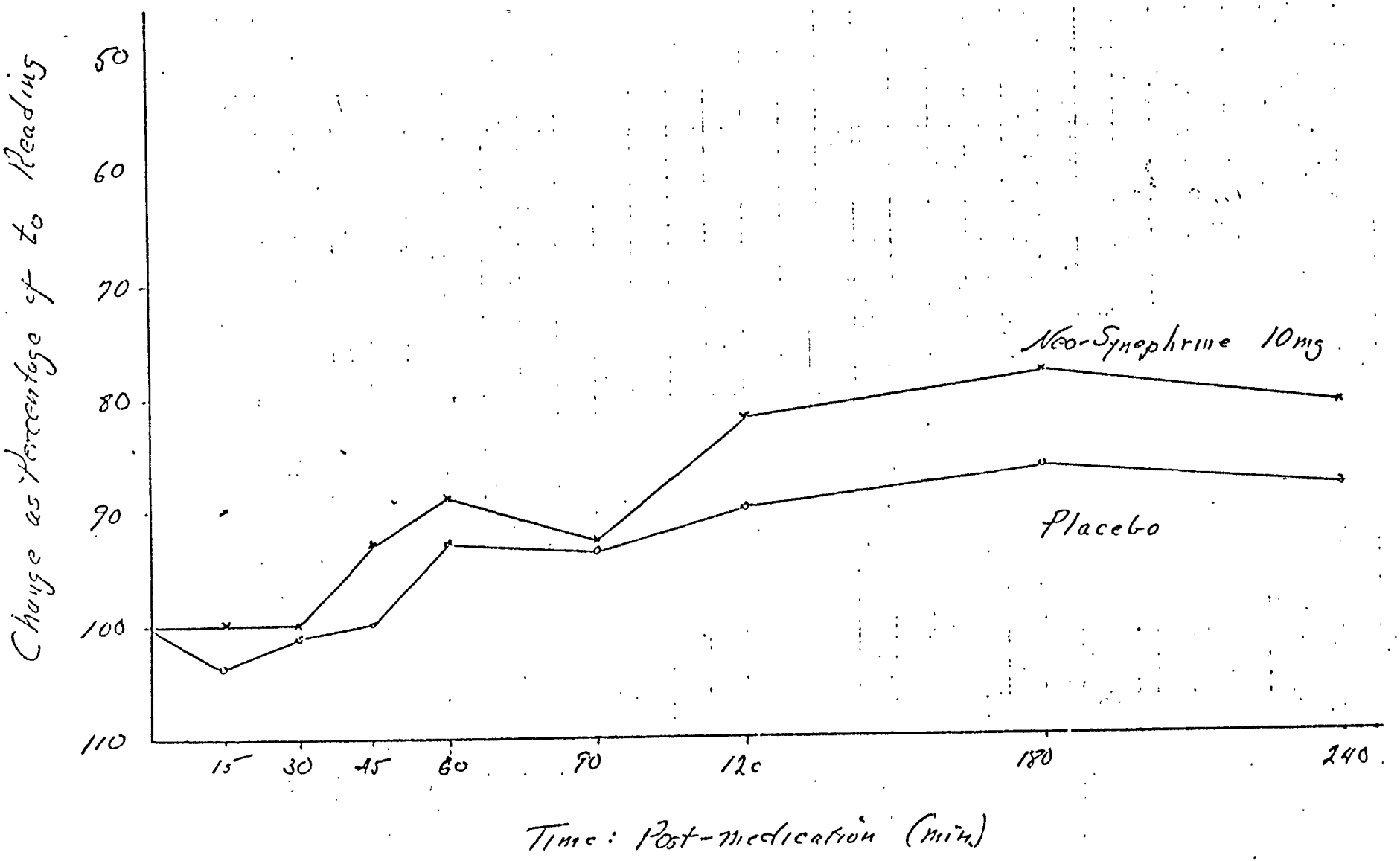
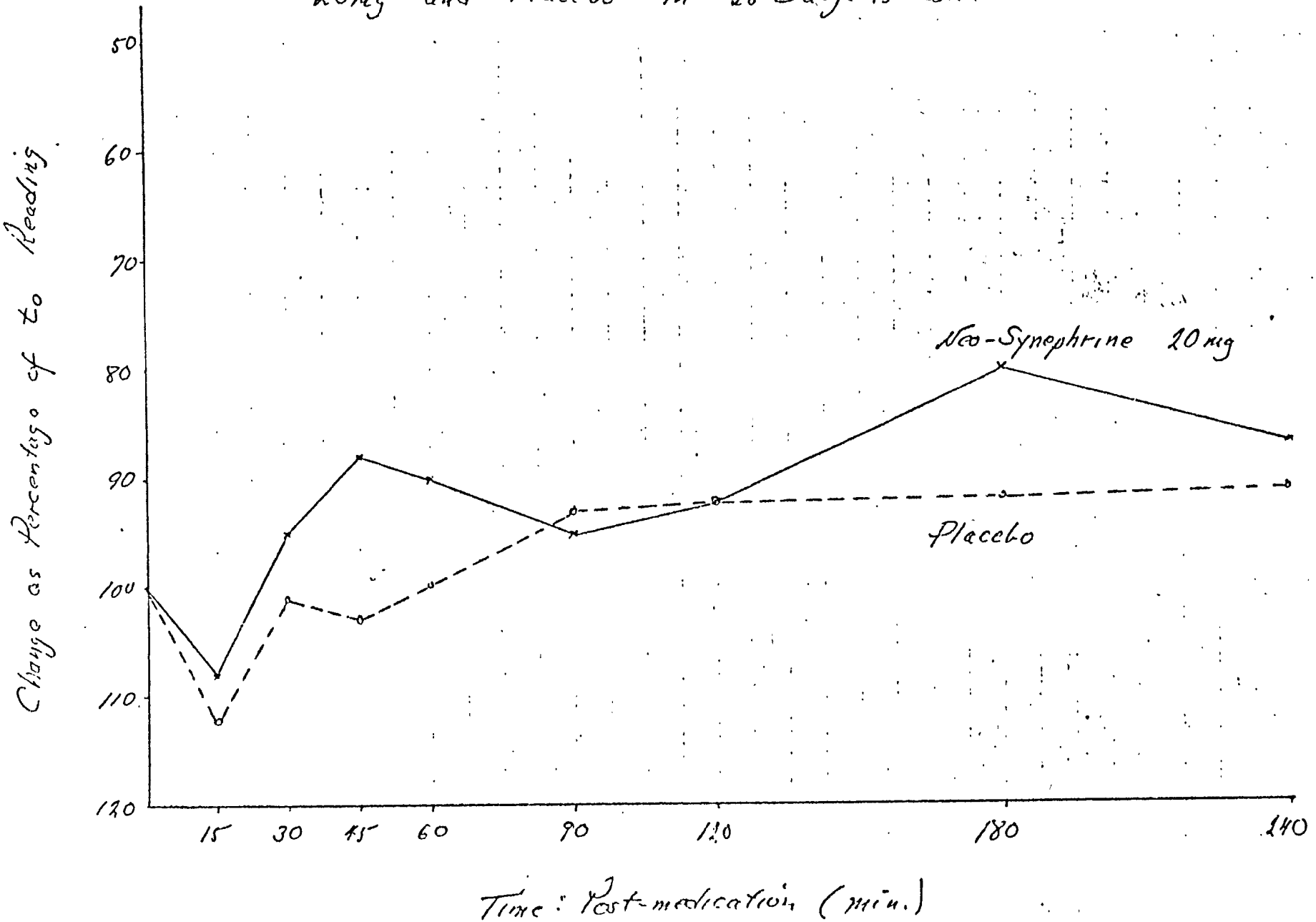


Figure 2

Comparison of the Nasal Decongestant Effect of Oral Neo-Synephrine 20mg and Placebo in 25 Subjects with "Common Cold"



Objective Measurement Means*
Neo-Synephrine (10 mg)

Patient	Treatment	t_0**	t_{15}***	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}	t_{180}	t_{240}
1	Drug	33.3	1.03	0.75	0.85	0.78	0.75	0.96	0.85	0.86
	Placebo	24.8	1.05	1.32	1.15	1.15	1.32	1.02	1.06	0.80
2	Drug	52.0	1.31	1.16	1.23	1.07	1.10	1.12	1.00	0.37
	Placebo	60.4	1.14	0.91	1.15	0.58	1.00	0.62	0.68	0.78
3	Drug	24.5	1.12	1.16	1.24	1.19	1.24	0.95	0.96	0.92
	Placebo	31.7	0.96	0.91	0.79	0.82	0.75	0.81	0.85	0.98
7	Drug	24.8	1.11	1.02	1.04	0.90	0.70	0.97	0.99	1.07
	Placebo	18.4	0.93	1.03	0.96	0.97	1.02	1.01	1.03	1.35
8	Drug	23.4	0.85	0.88	0.88	0.78	0.74	0.77	0.63	0.54
	Placebo	20.0	0.96	0.97	1.00	0.95	0.83	1.13	0.84	1.02
10	Drug	21.1	1.04	1.00	1.02	0.83	0.84	0.89	0.79	0.82
	Placebo	29.6	1.05	0.94	0.91	1.01	0.96	1.01	1.03	0.91
14	Drug	14.1	0.90	0.91	0.77	0.79	0.76	0.67	0.76	0.75
	Placebo	19.0	0.66	0.58	0.54	0.64	0.56	0.70	0.50	0.59
16	Drug	38.1	1.09	0.79	0.80	0.34	0.61	0.65	0.60	0.55
	Placebo	26.4	0.92	0.87	0.98	1.23	1.27	0.64	0.41	1.04
17	Drug	18.3	0.84	0.76	0.97	0.85	0.83	0.74	0.82	0.92
	Placebo	40.5	1.18	1.08	0.85	0.92	1.22	1.04	0.52	0.60
18	Drug	16.1	1.39	1.51	0.76	1.06	1.16	1.29	1.93	2.34
	Placebo	29.7	1.14	1.16	0.83	0.94	0.56	0.33	1.18	0.58
20	Drug	28.4	1.16	0.88	0.65	0.45	0.98	0.89	0.34	0.83
	Placebo	23.2	1.05	1.20	0.95	0.95	1.01	0.39	0.51	0.50
21	Drug	19.7	1.29	1.42	1.64	1.37	1.43	1.37	1.05	0.74
	Placebo	26.2	1.01	1.14	0.94	1.10	0.92	0.89	0.71	0.39
25	Drug	20.9	0.94	1.09	1.25	1.06	0.74	1.01	0.72	0.89
	Placebo	21.2	1.10	0.98	1.09	0.51	1.10	0.75	0.72	0.86
27	Drug	16.8	0.77	0.88	0.89	0.92	0.81	0.82	0.93	0.90
	Placebo	26.0	0.75	1.12	0.68	0.73	0.92	1.07	0.87	0.63

*Each number represents the mean of 5 measurements on both right and left nostrils.

t_0: premedication reading (units) *t_{15}, etc.: mean as % of t_0

APPENDIX

Objective Measurement Means*
Neo-Synephrine (10 mg)

Patient	Treatment	t_0**	t_{15}***	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}	t_{180}	t_{240}
28	Drug	34.5	1.02	0.95	1.13	1.08	1.26	1.31	1.03	1.30
	Placebo	27.3	1.39	1.11	1.26	1.26	1.28	1.13	1.44	1.30
30	Drug	36.6	0.80	0.41	0.51	0.85	0.56	0.69	0.61	0.47
	Placebo	27.6	0.94	1.00	0.57	0.58	0.55	0.60	0.43	0.57
31	Drug	19.5	1.19	1.14	1.11	0.91	0.92	0.93	0.86	0.88
	Placebo	27.3	1.00	0.96	1.03	1.00	0.91	0.87	0.87	0.91
33	Drug	9.9	1.21	1.38	1.08	1.05	1.49	0.80	0.95	0.62
	Placebo	13.0	1.20	1.30	0.80	0.99	1.00	0.95	0.98	0.93
34	Drug	13.3	1.10	1.38	0.97	1.13	1.17	0.88	0.89	0.89
	Placebo	13.4	0.99	0.83	1.11	0.72	0.93	0.57	0.38	0.84
36	Drug	28.1	1.02	0.93	1.20	0.68	0.99	0.58	0.38	0.41
	Placebo	32.2	1.03	1.15	1.10	0.94	0.57	0.50	0.54	0.62
41	Drug	29.2	0.68	0.84	0.83	0.78	0.55	0.49	0.51	0.44
	Placebo	27.7	0.77	0.67	0.71	0.63	0.73	0.48	0.46	0.52
42	Drug	78.2	1.11	1.13	1.22	1.22	1.05	1.05	1.08	1.14
	Placebo	75.6	1.05	0.94	0.96	0.93	1.07	0.96	1.04	0.92
44	Drug	23.0	1.17	1.19	1.36	1.29	1.09	1.12	1.05	1.12
	Placebo	25.9	1.10	1.07	1.20	1.03	1.29	1.12	1.00	0.92
48	Drug	25.9	0.95	0.87	0.69	0.87	0.77	0.70	0.69	0.97
	Placebo	33.3	0.84	0.84	0.66	0.67	0.54	0.85	0.66	0.51
50	Drug	19.7	0.97	0.84	0.77	0.89	1.03	0.90	1.01	1.22
	Placebo	16.2	0.94	1.09	1.04	1.03	1.02	1.03	0.87	1.07

*Each number represents the mean of 5 measurements on both right and left nostrils.

t_0: premedication reading (units) *t_{15}, etc.: mean as % of t_0

Objective Measurement Means*
Neo-Synephrine (20 mg)

Patient	Treatment	t_0**	t_{15}***	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}	t_{180}	t_{240}
4	Drug	13.5	1.52	0.94	1.05	1.24	1.27	1.15	1.14	1.18
	Placebo	19.6	0.93	0.68	0.67	0.69	0.80	0.58	0.83	0.78
5	Drug	22.8	1.16	0.58	0.82	0.98	1.62	0.78	0.82	1.02
	Placebo	28.3	0.88	0.50	0.62	0.64	1.05	1.07	0.89	0.69
6	Drug	34.0	1.18	0.91	0.71	0.85	0.39	0.91	0.82	0.80
	Placebo	42.5	0.77	0.70	0.48	0.62	0.69	0.95	0.36	0.79
9	Drug	18.0	1.11	1.09	0.94	0.84	0.79	0.56	0.65	0.55
	Placebo	19.5	1.52	1.17	1.16	1.09	0.69	0.72	0.46	0.74
11	Drug	38.5	1.23	1.22	1.16	1.17	0.70	0.69	0.75	1.06
	Placebo	35.8	1.08	1.06	0.90	0.91	1.14	1.18	0.84	0.99
12	Drug	9.8	1.02	0.86	0.98	1.29	1.01	0.96	0.92	0.88
	Placebo	11.2	0.91	0.96	0.95	0.95	1.03	0.93	1.01	0.44
13	Drug	26.3	0.78	0.86	0.82	0.95	0.69	1.21	1.32	0.80
	Placebo	28.2	0.82	0.61	0.59	0.72	0.91	0.93	0.66	0.80
15	Drug	20.7	1.50	1.60	1.13	0.95	0.88	0.94	0.84	0.90
	Placebo	12.6	2.18	1.58	1.75	1.59	1.98	1.50	1.97	1.91
19	Drug	13.6	1.19	1.24	0.98	1.07	1.01	0.92	0.93	0.78
	Placebo	16.6	0.98	0.90	0.99	1.06	1.22	1.00	1.36	1.63
22	Drug	16.3	0.99	1.13	1.13	0.62	0.51	0.59	1.18	0.73
	Placebo	17.4	1.20	1.24	0.70	1.08	1.03	1.07	0.43	1.08
23	Drug	29.4	1.09	0.86	0.89	1.03	1.07	1.03	0.70	0.73
	Placebo	27.8	1.06	1.05	0.70	0.92	1.02	1.39	0.64	0.81
24	Drug	29.5	1.25	0.47	0.92	1.00	0.80	0.91	0.35	0.91
	Placebo	37.0	1.15	0.81	0.87	1.11	1.04	1.14	0.64	0.60
26	Drug	25.2	1.06	0.96	1.36	0.85	0.55	0.82	0.41	0.60
	Placebo	28.4	1.02	1.21	0.83	0.57	0.76	1.01	0.96	0.78
29	Drug	53.7	0.76	0.91	0.80	0.71	0.64	0.56	0.56	0.60
	Placebo	28.2	1.00	0.90	0.97	1.05	0.98	0.92	0.96	0.98

*Each number represents the mean of 5 measurements on both right and left nostrils.

t_0: premedication reading (units) *t_{15}, etc.: mean as % of t_0

Objective Measurement Means*
Neo-Synephrine (20 mg)

Patient	Treatment	t_0**	t_{15}***	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}	t_{180}	t_{240}
32	Drug	4.2	1.28	1.87	1.85	1.92	1.80	1.60	1.69	2.18
	Placebo	13.2	0.88	0.96	1.02	0.72	0.69	0.61	0.63	0.83
35	Drug	30.2	0.91	0.83	0.66	0.82	0.52	0.55	0.64	0.51
	Placebo	29.7	1.03	0.97	0.85	0.74	0.94	0.66	0.21	0.50
38	Drug	32.1	1.13	1.11	1.19	1.03	1.15	1.21	0.92	0.86
	Placebo	45.9	1.00	1.06	0.96	0.95	0.76	0.82	0.76	0.82
39	Drug	18.8	0.95	0.85	1.06	0.99	0.99	0.94	0.94	1.22
	Placebo	19.6	1.02	0.88	0.95	0.85	0.93	0.94	0.83	0.85
40	Drug	34.3	0.93	0.89	0.99	0.84	0.70	0.68	0.73	0.96
	Placebo	28.7	1.03	0.98	0.99	1.03	1.12	0.93	1.09	0.78
43	Drug	25.4	1.21	0.80	0.93	0.76	0.93	1.13	1.21	0.87
	Placebo	21.3	1.08	0.61	0.75	0.61	0.31	0.59	0.48	0.59
45	Drug	13.7	1.11	1.18	1.05	0.97	1.04	0.92	0.91	0.79
	Placebo	12.9	0.97	0.79	0.80	0.70	0.75	0.46	0.40	0.70
46	Drug	10.1	1.38	1.38	1.43	1.28	1.37	1.43	1.31	1.10
	Placebo	11.2	1.34	1.21	1.28	1.36	1.43	1.31	1.21	1.30
47	Drug	28.9	0.95	0.61	0.80	1.07	0.93	0.80	1.18	0.92
	Placebo	27.5	1.01	0.85	0.55	0.83	0.53	0.49	0.63	0.52
49	Drug	29.4	1.15	1.11	1.00	0.81	0.89	0.84	1.06	0.84
	Placebo	26.7	1.05	1.07	0.80	0.90	1.02	0.97	0.93	0.85

*Each number represents the mean of 5 measuremtnts on both right and left nostrils.

t_0: premedication reading (units) *t_{15}, etc.: mean as % of t_0

REFERENCE 7

INTER-OFFICE MEMORANDUM

STERLING-WINTHROP RESEARCH INSTITUTE

RENSSELAER, NEW YORK

April 10, 1969

Memo to: Dr. Blackmore

From: N. A. Hulme

Re: Oral Neo-Synephrine - Cintest Labs Study No. 1

The results of the study completed a year ago (Hulme to Wessinger January 12, 1968) by Elizabeth Biochemical Labs demonstrated that Neo-Synephrine when taken orally in doses as low as 10 mg produced significant improvement in nasal congestion when measured both by objective and subjective means. As a result of these findings additional studies were set up both for the purpose of exploring more fully the dosage spectrum of orally administered Neo-Synephrine and secondly in order to confirm the earlier data by means of studies carried out at additional laboratories.

One of two of these confirmatory studies was conducted by the Cintest Division of Hill Top Laboratories of Cincinnati. Details of the study and a detailed statistical analysis of the results carried out by Mr. Stander are presented below.

Protocol and Methodology

A total of 48 volunteer subjects complaining of head colds and having confirmed nasal congestion on two consecutive days participated in the study. Objective evaluation of degree of nasal congestion was carried out using the Blanchard et al (E.E.N.T. Monthly 43, 76-82, 1964) modification of the Butler-Ivy method.

The subjects were assigned coded drugs on a double-blind randomized basis. The randomization was designed so that half the subjects in each dose category received placebo on the first day and active medication on the second day. The reversed sequence occurred with the other subjects. The following table gives the number of subjects receiving each of the drugs.

No. of Subjects	Neo-Synephrine vs. Placebo	Phenylpropanolamine vs. Placebo
16	10 mg	-
16	25 mg	-
16	-	50 mg

All drugs were supplied in identical capsules and packaged in individual preassigned envelopes labeled by code number and subject number.

Objective measurements of airflow resistance were carried out by obtaining five consecutive readings for each nostril at 0, 15 and 30 minutes before medication and 15, 30, 45, 60, 120 and 240 minute intervals following medication. The ten readings from both nostrils were combined and the arithmetic means employed for further calculations and analysis.

Subjective impressions of changes in nasal congestion were obtained by having each subject describe his congestion at the time of each set of airflow measurements were made as being closest to one of the following conditions.

Degree of Congestion

Nose feels clear
Almost clear
Stuffy
Very stuffy
Completely blocked

A shift of one degree of congestion from the premedication state was graded as plus or minus 1, a shift in two degrees as plus or minus 2, etc. The sums of the changes at each time interval was recorded for each subject. The median change for all subjects on each active medication dosage was compared to the same subjects placebo scores for significance of the difference.

Results

The mean of the air resistance readings for each subject was calculated as the percent (fractional units x 100) change from the last premedication reading (see Appendix). The combined data was then analyzed for signifiance between the placebo and medication groups at each of the time intervals. The levels of signifiance for each of the drugs at the indicated time interval are given in Table I. The data plotted as graphs for each dosage: placebo pair are given in Figures 1 to 3. As will be noted periods of significant differences occurred at 90 to 180 minutes only following medication with the 10 mg dose of Neo-Synephrine, at 120 to 240 minutes following the 25 mg Neo-Synephrine dose and between 60 and 120 minutes following the 50 mg dose of phenylpropanolamine.

A comparison was made of the sum of the subjective difference changes seen in the degree of congestion for each of the medications. These differences with the levels of statistical significance between treatments for the drug:placebo pairs are given in Tables II to IV. Significant changes in congestion occurred at the 10 mg

dose of Neo-Synephrine and at 50 mg of phenylpropanolamine but not with the 25 mg level of Neo-Synephrine.

Discussion

One of the primary reasons for this study was to try to confirm the fact as reported earlier by Elizabeth Biochemical Labs that orally administered Neo-Synephrine does produce significant nasal decongestion. As can be seen the results obtained do support the qualitative results of the Elizabeth Biochemical Labs study. A second finding of importance is that a 10 mg oral dose of Neo-Synephrine, again in agreement with Elizabeth Biochemical Labs, does produce a significant improvement in nasal airflow and correlates with subjective feeling of lessened nasal congestion.

The reason for the period of decreased air resistance with the three placebo groups is not clear although it may reflect the change in environment which occurs when subjects are brought into the area where the measurements are made. Other factors such as operator technique may also play a role.

In terms of the raw data itself there appears to be greater variability in the system than in the previous study. This is not entirely unexpected as this is the first study of this type carried out by Cintest and a certain amount of technical know-how in handling the instrument had to be learned during the actual study. The inherent variability in this study also probably accounts for the failure to show subjective significance at the 25 mg dose; whereas, it was demonstrated at the 10 mg dose of Neo-Synephrine and with the 50 mg dose of phenylpropanolamine. It would be expected that subsequent studies with Cintest using this procedure would be carried out with a greater degree of precision.

N. A. Hulme

bjc

cc: Dr. Wessinger
Dr. Luduena
Mr. Stander
Dr. Cox
Dr. Surrey
Mr. Heike
Dr. Gerding
Dr. Rees
Dr. Giambalvo
File (3)

Table I

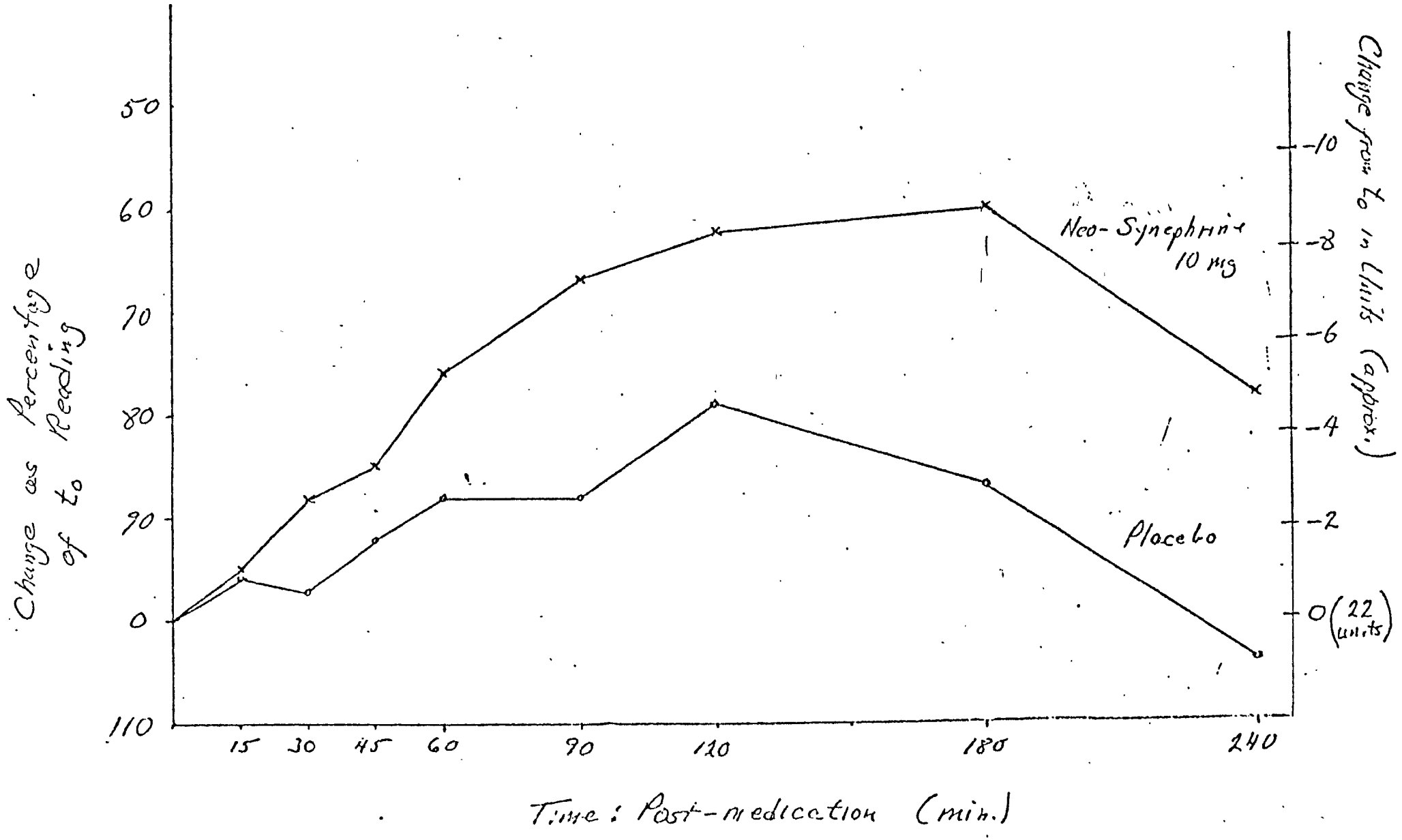
COMPARISON OF THE NASAL DECONGESTANT EFFECT OF ORAL PHENYLPROPANOLAMINE (50 mg) AND NEO-SYNEPHRINE (10 mg, and 25 mg) VERSUS PLACEBO IN SUBJECTS WITH "COMMON COLD"

Objective Measurements (fractional units x 100)

	t_0 (units)	t_{15}/t_0	t_{30}/t_0	t_{45}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0	t_{180}/t_0	t_{240}/t_0
Neo-Synephrine (10 mg)	22.3	95	88	85	76	67	62	60	78
Placebo	20.6	96	97	92	88	87	79	87	104
Analysis of Variance Comparison between treatments (n = 16)	p>0.1 (s=7.3)	p>0.1 (s=12)	p>0.1 (s=14)	p>0.1 (s=16)	p>0.1 (s=21)	p=0.025 (s=21)	p=0.05 (s=23)	p=0.025 (s=27)	p>.1 (s=42)
Neo-Synephrine (25 mg)	20.4	93	85	79	72	66	54	55	77
Placebo	17.6	96	96	86	82	77	74	85	102
Analysis of Variance Comparison between treatments (n = 16)	p>0.1 (s=5.4)	p>0.1 (s=14)	p>0.1 (s=22)	p>0.1 (s=23)	p>0.1 (s=21)	p>0.1 (s=22)	p=0.025 (s=22)	p<0.01 (s=22)	p=0.05 (s=30)
Phenylpropanolamine (50 mg)	21.1	94	85	81	71	64	54	60	88
Placebo	22.7	101	91	87	83	78	71	68	97
Analysis of Variance Comparison between treatments (n = 15)	p>0.1 (s=4.1)	p>0.1 (s=12)	p>0.1 (s=13)	p>0.1 (s=18)	p≅0.1 (s=20)	p=0.05 (s=17)	p=0.025 (s=18)	p>0.1 (s=23)	p>0.1 (s=45)

Figure 1

Comparison of the Nasal Decongestant Effect of Oral Neo-Synephrine 10 mg and Placebo in 16 Subjects with "Common Cold"



Figure

Comparison of the Nasal Decongestant Effect of Oral Neo-Synephrine 25 mg and Placebo in 16 Subjects with "Common Cold"

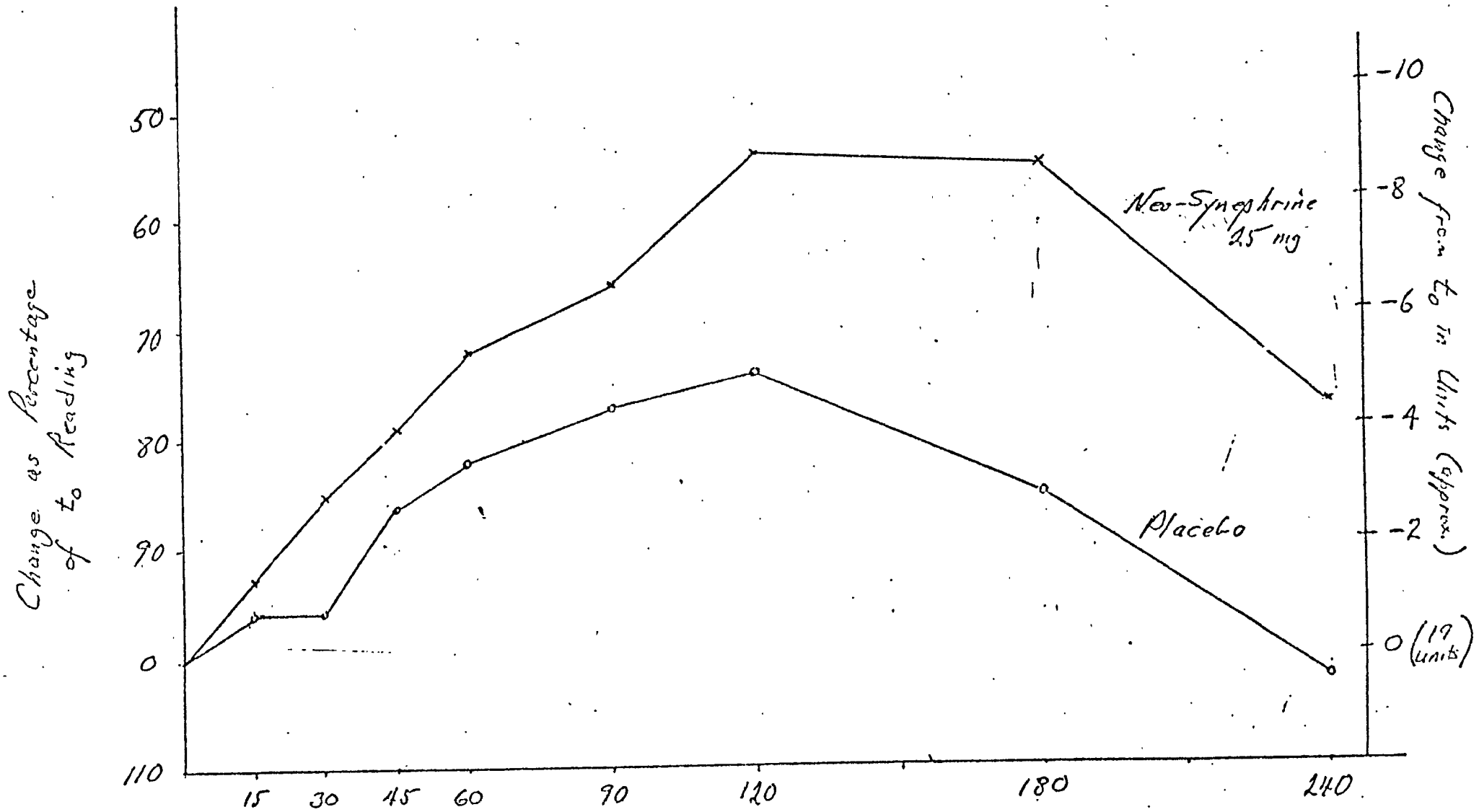


Fig 3

Comparison of the Nasal Decongestant Effect of Oral Phenylpropanolamine 50mg and Placebo in 16 Subjects with "Common Cold"

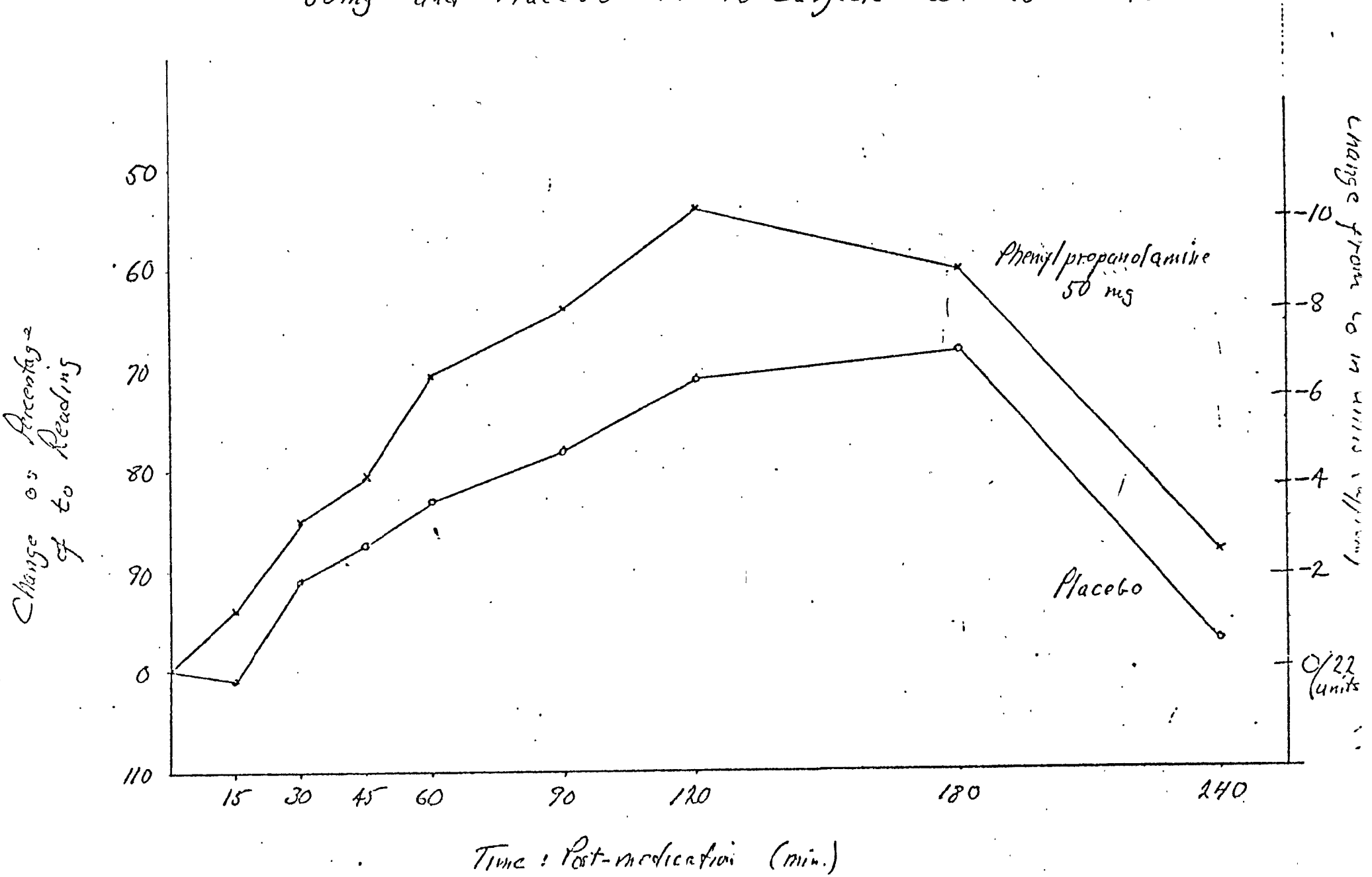


Table II

COMPARISON OF THE NASAL DECONGESTANT EFFECT OF ORAL NEO-SYNEPHRINE (10 mg) AND PLACEBO IN 16 SUBJECTS WITH "COMMON COLD"

Sum of the Subjective Impression Differences

Patient	Neo-Synephrine (10 mg)	Placebo
1	-6	0
3	-8	0
5	-7	0
8	-2	-6
9	-7	-8
15	-5	0
18	-4	0
23	0	0
26	-11	-6
32	-12	-4
36	-9	-13
39	-5	0
41	-5	-10
44	-7	-4
46	-7	-5
48	-10	-10
Median	-7	-4

Significance of the difference between treatments; p=0.05
Wilcoxon Matched-Pairs Signed-Ranks test

Table III

COMPARISON OF THE NASAL DECONGESTANT EFFECT OF ORAL NEO-SYNEPHRINE (25 mg) AND PLACEBO IN 16 SUBJECTS WITH "COMMON COLD"

Sum of the Subjective Impression Differences

Patient	Neo-Synephrine (25 mg)	Placebo
10	-5	0
11	-8	-14
12	-6	-2
13	-7	-7
14	-3	0
20	-5	-8
21	-4	0
22	-4	-4
25	-4	0
28	-6	-5
29	-3	-11
30	-10	-2
37	-7	-10
40	-12	-4
45	-6	-13
47	-8	-10
Median	-6	-4.5

Significance of the difference between treatments; $p>0.1$
Wilcoxon Matched-Pairs Signed-Ranks test

Table IV

COMPARISON OF THE NASAL DECONGESTANT EFFECT OF ORAL PHENYLPROPANOLAMINE (50 mg) AND PLACEBO IN 15 SUBJECTS WITH "COMMON COLD"

Sum of the Subjective Impression Differences

Patient	Phenylpropanolamine (50 mg)	Placebo
4	-4	-5
6	-8	-3
7	-11	-2
16	-4	-2
17	-6	0
19	-8	0
24	-6	0
27	-6	-3
31	-10	-2
33	-10	-14
34	-8	0
35	-13	-11
38	-5	-4
42	-9	-5
43	-8	-8
Median	-8	-3

Significance of the difference between treatments; p=0.01
Wilcoxon Matched-Pairs Signed-Ranks test

APPENDIX

Objective Measurement Means*
Neo-Synephrine (10 mg)

Patient	Treatment	t_0 **	t_{15} ***	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}	t_{180}	t_{240}
1	Drug	44.4	0.90	0.73	0.65	0.44	0.49	0.43	0.34	0.27
	Placebo	25.8	0.92	1.02	0.93	1.01	0.99	0.98	1.02	1.00
3	Drug	19.4	0.68	0.68	0.54	0.53	0.63	0.63	0.61	0.56
	Placebo	19.7	1.00	0.94	0.90	0.82	0.94	0.86	1.24	0.86
5	Drug	34.6	0.92	0.64	0.79	0.64	0.46	0.52	0.42	0.29
	Placebo	26.5	1.01	1.02	1.02	0.99	1.05	1.00	0.99	1.00
8	Drug	14.1	0.98	0.91	0.73	0.68	0.59	0.55	0.47	0.39
	Placebo	30.2	0.76	0.84	0.86	0.68	0.67	0.72	0.66	0.63
9	Drug	18.5	0.96	0.95	0.88	0.68	0.76	0.73	0.53	0.54
	Placebo	17.1	0.94	0.97	0.73	0.66	0.69	0.72	0.64	0.53
15	Drug	18.9	0.96	0.92	0.92	0.81	0.74	0.69	0.42	0.32
	Placebo	11.7	1.09	1.12	1.07	1.00	1.04	0.99	0.89	0.73
18	Drug	47.4	0.94	0.86	0.94	0.98	0.98	0.46	0.52	0.45
	Placebo	26.6	0.80	0.82	0.76	0.76	0.75	0.75	0.73	0.73
23	Drug	13.1	1.07	1.15	1.16	1.16	1.02	1.15	1.11	1.47
	Placebo	23.8	0.98	0.97	1.00	1.04	1.03	0.94	0.94	2.21
26	Drug	12.5	0.89	0.89	0.84	0.82	0.73	0.53	0.53	2.05
	Placebo	26.3	1.02	1.25	1.30	1.41	1.45	1.38	1.45	0.95
32	Drug	16.5	0.85	0.79	0.69	0.59	0.57	0.60	0.56	0.82
	Placebo	16.9	1.12	1.06	1.09	1.07	0.95	0.72	0.68	1.10
36	Drug	21.4	1.01	0.97	0.92	0.58	0.40	0.43	0.39	0.56
	Placebo	11.8	1.12	0.97	0.82	0.88	0.85	0.43	0.39	1.55
39	Drug	32.2	0.89	0.85	0.85	0.77	0.64	0.53	0.45	0.55
	Placebo	23.1	1.11	1.07	1.07	1.02	1.12	1.11	1.28	1.27
41	Drug	13.8	0.98	0.92	0.86	0.82	0.50	0.45	0.79	0.99
	Placebo	12.3	0.90	0.79	0.73	0.53	0.50	0.45	0.92	1.37
44	Drug	25.9	0.98	0.98	0.98	0.88	0.66	0.75	0.85	1.14
	Placebo	29.5	0.83	0.90	0.78	0.62	0.52	0.36	0.55	0.61
46	Drug	11.0	1.04	0.97	1.00	0.91	0.76	0.62	1.03	1.51
	Placebo	15.4	0.89	0.86	0.84	0.78	0.74	0.67	0.65	0.71
48	Drug	13.1	1.10	0.95	0.87	0.80	0.78	0.79	0.66	0.62
	Placebo	13.1	0.95	0.87	0.85	0.75	0.63	0.58	0.84	1.36

*Each number represents the mean of 5 measurements on both right and left nostrils.

t_0: premedication reading (units) *t_{15}, etc.: mean as % of t_0

APPENDIX

Objective Measurement Means*
Neo-Synephrine (25 mg)

Patient	Treatment	t_0 **	t_{15} ***	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}	t_{180}	t_{240}
10	Drug	23.4	1.02	1.01	1.12	0.70	0.72	0.64	0.61	0.52
	Placebo	21.8	1.10	1.05	1.02	1.07	1.08	0.96	0.99	1.01
11	Drug	19.0	0.96	0.75	0.71	0.67	0.74	0.57	0.52	0.47
	Placebo	35.8	0.74	0.74	0.44	0.45	0.46	0.34	0.34	0.28
12	Drug	38.3	0.79	0.64	0.52	0.60	0.58	0.46	0.49	0.39
	Placebo	20.5	0.98	1.20	1.01	0.96	1.05	1.05	1.05	1.05
13	Drug	18.3	0.67	0.54	0.49	0.45	0.48	0.39	0.34	0.30
	Placebo	11.2	0.94	0.96	0.96	0.91	0.95	0.83	0.80	0.82
14	Drug	13.5	1.25	1.15	1.16	1.12	0.92	0.81	0.74	0.67
	Placebo	12.4	0.94	0.85	0.80	0.78	0.72	0.73	0.76	0.78
20	Drug	12.4	0.87	0.83	0.77	0.74	0.80	0.60	0.54	0.62
	Placebo	10.7	0.85	0.78	0.60	0.67	0.69	0.67	0.67	0.62
21	Drug	34.2	1.03	1.02	0.88	0.69	0.57	0.46	0.33	0.24
	Placebo	36.4	1.31	1.31	1.40	1.30	1.43	1.34	1.30	1.06
22	Drug	41.0	0.96	0.87	0.70	0.68	0.52	0.40	0.37	0.35
	Placebo	25.5	0.72	0.62	0.60	0.63	0.61	0.83	0.86	0.53
25	Drug	18.8	1.00	0.97	0.95	0.91	0.88	0.52	0.24	1.08
	Placebo	20.7	1.01	0.98	0.97	1.02	1.04	0.96	0.99	1.28
28	Drug	18.2	0.94	0.54	0.54	0.54	0.56	0.54	0.46	0.58
	Placebo	11.6	0.90	0.78	0.80	0.74	0.54	0.64	0.48	1.26
29	Drug	19.9	1.01	1.08	0.95	0.76	0.62	0.61	0.83	0.94
	Placebo	13.0	0.82	0.78	0.66	0.56	0.53	0.46	1.09	1.67
30	Drug	12.4	0.75	0.69	0.60	0.67	0.62	0.46	0.42	1.55
	Placebo	12.7	1.16	1.48	1.22	1.16	0.85	0.77	0.73	1.08
37	Drug	14.2	0.92	0.86	0.78	0.71	0.64	0.57	0.39	1.65
	Placebo	11.4	0.91	0.99	0.83	0.89	0.75	0.80	0.73	1.27
40	Drug	13.9	0.95	0.81	0.73	0.76	0.58	0.45	1.11	1.18
	Placebo	11.8	1.00	0.98	0.91	0.92	0.66	0.60	0.99	0.93
45	Drug	14.0	0.91	0.89	0.81	0.79	0.65	0.54	0.64	0.80
	Placebo	11.9	1.12	1.08	0.92	0.59	0.53	0.52	1.10	1.55
47	Drug	14.5	0.84	0.93	0.88	0.73	0.68	0.60	0.74	1.02
	Placebo	14.9	0.85	0.73	0.62	0.54	0.44	0.41	0.78	1.08

*Each number represents the mean of 5 measurements on both right and left nostrils.

t_0: premedication reading (units) *t_{15}, etc.: mean as % of t_0

APPENDIX

Objective Measurement Means*
Phenylpropanolamine (50 mg)

Patient	Treatment	t_0 **	t_{15} ***	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}	t_{180}	t_{240}
4	Drug	47.4	0.94	0.92	0.94	0.94	0.77	0.63	0.64	0.63
	Placebo	44.1	0.95	0.73	0.71	0.60	0.52	0.54	0.48	0.49
6	Drug	12.4	1.01	1.06	1.05	0.91	0.82	0.94	0.70	0.52
	Placebo	12.4	1.20	1.04	1.17	0.78	0.90	0.87	0.91	0.88
7	Drug	15.3	1.11	0.91	0.96	0.69	0.63	0.56	0.53	0.36
	Placebo	16.3	0.98	0.92	0.77	0.70	0.58	0.58	0.45	0.30
16	Drug	26.9	1.13	0.96	0.82	0.72	0.62	0.52	0.48	0.39
	Placebo	28.8	1.02	0.84	0.76	0.56	0.56	0.70	0.72	0.65
17	Drug	25.3	0.93	0.76	0.48	0.32	0.32	0.63	0.57	0.42
	Placebo	37.5	0.94	1.03	1.00	0.97	0.96	0.91	0.81	0.78
19	Drug	24.0	0.85	0.66	0.84	0.80	0.78	0.39	0.51	0.57
	Placebo	34.4	1.30	0.94	1.14	1.19	1.20	1.19	1.14	1.12
24	Drug	25.6	0.98	0.97	0.95	0.90	0.78	0.51	0.33	0.73
	Placebo	28.2	0.99	1.01	0.99	0.98	0.98	0.96	0.96	0.89
27	Drug	22.3	0.96	0.85	0.80	0.69	0.65	0.57	0.44	0.60
	Placebo	9.7	0.87	0.72	0.73	0.72	0.69	0.75	0.50	1.76
31	Drug	12.4	0.96	0.64	0.69	0.63	0.47	0.35	0.35	0.90
	Placebo	12.8	0.86	0.88	0.86	0.92	0.72	0.60	0.64	0.87
33	Drug	12.1	0.93	0.96	0.87	0.79	0.79	0.50	0.54	1.40
	Placebo	15.9	1.02	0.99	0.70	0.74	0.73	0.38	0.32	0.89
34	Drug	26.6	0.81	0.74	0.68	0.69	0.62	0.57	0.57	0.64
	Placebo	30.6	0.85	0.96	0.90	0.91	0.88	0.82	0.86	0.88
35	Drug	16.2	0.86	0.74	0.64	0.58	0.58	0.41	0.35	1.03
	Placebo	13.8	0.90	0.83	0.66	0.68	0.62	0.43	0.33	2.30
38	Drug	15.3	1.03	1.06	1.08	0.90	0.84	0.90	0.74	1.26
	Placebo	17.4	1.02	0.81	0.73	0.79	0.72	0.72	0.62	0.72
42	Drug	16.4	0.78	0.70	0.60	0.45	0.44	0.32	1.34	1.92
	Placebo	14.6	1.20	1.03	1.09	1.04	0.90	0.70	0.85	1.20
43	Drug	17.9	0.88	0.84	0.75	0.65	0.44	0.38	0.98	1.84
	Placebo	24.1	1.03	0.89	0.87	0.94	0.67	0.53	0.63	0.84

*Each number represents the mean of 5 measurements on both right and left nostrils.

t_0: premedication reading (units) *t_{15}, etc.: mean as % of t_0

REFERENCE 8

STERLING-WINTHROP RESEARCH INSTITUTE

MEDICAL RESEARCH DIVISION

Ref # 23

January 23, 1970

To: Dr. Blackmore

From: N. A. Hulme

Re: Oral Neo-Synephrine - Cintest Study No. 2

Following the successful completion of an earlier decongestant study, a second study was initiated (approved 4-14-69) with the Cintest Division of Hill Top Research, Inc., in which orally administered Neo-Synephrine in dosages of 10, 15 and 20 mg were compared to placebo and evaluated for nasal decongestant activity. The purpose was to further expand the range of dosages tested to include 20 mg and to accumulate additional numbers of subjects at the 10 and 15 mg levels.

Protocol and Methodology

A total of 48 subjects with head colds and having confirmed nasal congestion on two consecutive days participated in the study. Evaluation of the degree of nasal congestion was made by measuring the relative resistance to a constant flow of air passing through the nasal passageway by a modification of the Butler-Ivy procedure (Blanchard et al E.E.N.T. Monthly 43, 76-82, 1964).

The subjects were assigned coded drugs on a double-blind randomized basis. The randomization was designed so that half the subjects in each dose category received placebo on the first day and active medication on the second day. The reversed sequence occurred with the other subjects. The following table gives the number of subjects receiving each of the drugs.

No. of Subjects	Neo-Synephrine vs. Placebo
16	10 mg
16	15 mg
16	20 mg

All drugs were supplied in identical capsules and packaged in individual preassigned envelopes labeled by code number and subject number.

Objective measurements of airflow resistance were carried out by obtaining five consecutive readings for each nostril at 0, 15 and 30 minutes before medication and 15, 30, 45, 60, 120 and 240 minute intervals following medication. The ten readings from both nostrils were combined and the arithmetic means employed for further calculations and analysis.

Subjective impressions of changes in nasal congestion were obtained by having each subject describe his congestion at the time each set of airflow measurements were made. These were classified as being closest to one of the following conditions:

Degree of Congestion
Nose feels clear
Almost clear
Stuffy
Very stuffy
Completely blocked

A shift of one degree of congestion from the premedication state was graded as plus or minus 1, a shift in two degrees as plus or minus 2, etc. The sums of the change at each time interval were recorded for each subject. The median change for all subjects on each active medication dosage was compared to the same subject's placebo scores for significance of the difference.

Pulse and sitting blood pressure readings were obtained on each subject at 30, 15 and 0 minutes before medication and at 30, 60, 90, 120, 180, and 240 minutes following medication. The readings from each medication group were combined and the arithmetic means employed for further calculations and analysis. This provided comparisons between active medication and placebo for diastolic pressure, systolic pressure and pulse rate.

Results and Discussion

The individual subject's air resistance measurment figures (see Appendix) were used to calculate arithmetic differences between premedication and postmedication results at indicated specific time intervals. These data were analyzed by Mr. Stander's group for significance between the placebo and medication readings. The mean values and the degree of significance at each of the dosages are given in Table I.

Analysis of the scores for the subjective impressions of decongestion were carried out. The mean values and the degree of significance are given in Table II.

The data indicates that no statistically significant differences occurred between placebo and any of the three Neo-Synephrine dosages by either the objective or subjective means of measurement.

The reason for the failure to obtain significant differences in this study is not obvious, particularly since this followed a previous study by the same group in which significant differences between placebo and Neo-Synephrine at 10 and 25 mg doses were found (Hulme to Blackmore 4-10-69). Upon discussing possible causes of failure of this study with the Cintest group, it became apparent that no evident change in conditions had occurred; that is, the same instrument was used, the same two technicians operated the instrument, the source of subjects and other obvious factors were not different. Since changes in technique could possibly have taken place that

the Cintest group was unconsciously not aware of, several steps were taken to check on this possibility having occurred. These included:

1. Analysis of the data by individual technician to determine whether lack of competency by one or the other lowered the overall significance of the study. Results showed no significant difference regardless of which technician operated the instrument.

2. Because of their considerable experience with the Butler-Ivy technique, a meeting was held with Mr. Boffa of the Elizabeth Biochemical Laboratories to discuss the problem and possibly turn up some overlooked but critical step. Again nothing obvious resulted that would explain the discrepancy.

3. Personal observation of one of the technicians was made (Charles Gaines) during testing of four subjects (subsequent study) to see whether some critical step was inadvertantly being overlooked. This operator's technique appeared sound with no obviously omitted steps.

4. The possibility of a drug mix-up was considered. Two left over capsules were obtained from Cintest and submitted blindly for chemical analysis. Both analyses were correct according to the code for the study.

Inasmuch as the objective as well as the subjective analysis failed to show differences, the possibility of some more basic problem than simple instrument or technician failure was considered. Such causes could include failure to fast before receiving medication, failure to take medication, improper selection of patients or even presence of a viral infection not amenable to drug treatment. Discussion with Mr. Wild and others of Cintest indicated that proper selection and drug administration were carried out but that poor control on the fasting requirement was maintained; that is, subjects (prison population) were asked to fast but no actual observation was made insuring that this step had been followed. If indeed the subjects were eating surreptitiously, it could explain the failure to find differences by markedly slowing down the rate of drug absorption. (This point has been corrected in the subsequent study). Other possibilities not considered could, of course, be operating and produce the results observed.

In summary, overall consideration of the problem and of the investigation into its cause yields no ready answer. There was no obvious failure in technique, but failure to insure premedication fasting on the part of the prisoner subjects could account for the lack of significance if this step had been omitted.

Analyses of the pulse rate data and diastolic and systolic blood pressure readings showed no significant differences between placebo and Neo-Synephrine at any of the postmedication time readings. Inasmuch as these measurements would be independent of other factors (drug administration failure excluded), the data obtained may be considered to be valid and a useful result of the study. The mean values and the degree of significance at each of the dosages are given in Tables III to V.

N. A. Hulme

bjc
Attachments

cc: Dr. Wessinger, Dr. Luduena, Mr. Stander, Dr. Cox, Dr. Surrey, Mr. Meike, Dr. Gerding, Dr. Rees, File

Table I

COMPARISON OF THE NASAL DECONGESTANT EFFECT OF ORAL NEO-SYNEPHRINE (10 mg, 15 mg, 20 mg) VERSUS PLACEBO IN SUBJECTS WITH COMMON COLD

Objective Measurements (fractional units)

	t_0	t_{15}/t_0	t_{30}/t_0	t_{45}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0	t_{180}/t_0	t_{240}/t_0
Neo-Synephrine 10 mg	28.0	.97	.94	.91	.85	.85	.80	.75	.72
Placebo	26.7	.96	.93	.90	.91	.85	.78	.73	.69
Analysis of Variance (s) (n = 15)	p>0.05 s=4.76	p>0.05 s=0.09	p>0.05 s=0.08	p>0.05 s=0.12	p>0.05 s=0.17	p>0.05 s=0.20	p>0.05 s=0.23	p>0.05 s=0.28	p>0.05 s=0.34
Neo-Synephrine 15 mg	25.0	.97	.93	.90	.86	.83	.74	.68	.58
Placebo	24.4	1.14	.96	.96	.92	.88	.83	.75	.70
Analysis of Variance (s) (n = 16)	p>0.05 s=2.56	p>0.05 s=0.44	p>0.05 s=0.10	p>0.05 s=0.12	p>0.05 s=0.09	p>0.05 s=0.12	p>0.05 s=0.18	p>0.05 s=0.23	p>0.05 s=0.29
Neo-Synephrine 20 mg	23.5	1.00	.98	.99	.92	.92	.84	.79	.73
Placebo	24.1	.98	.98	.97	.94	.93	.84	.74	.63
Analysis of Variance (s) (n = 15)	p>0.05 s=2.50	p>0.05 s=0.10	p>0.05 s=0.14	p>0.05 s=0.11	p>0.05 s=0.13	p>0.05 s=0.18	p>0.05 s=0.24	p>0.05 s=0.35	p>0.05 s=0.38

Table II

COMPARISON OF THE NASAL DECONGESTANT EFFECT OF ORAL NEO-SYNEPHRINE (15 mg, 20 mg, 25 mg) VERSUS PLACEBO IN SUBJECTS WITH COMMON COLD

Subjective Impression Differences

	Median Differences	Analysis of Variance	Number of Subjects
Neo-Synephrine 10 mg	-2.00	$p > 0.05$	15
Placebo	-3.87	s=4.18	
Neo-Synephrine 15 mg	-4.12	$p > 0.05$	16
Placebo	-3.81	s=2.86	
Neo-Synephrine 20 mg	-4.13	$p > 0.05$	15
Placebo	-2.93	s=3.32	

Table III

COMPARISON OF THE EFFECT OF ORAL NEO-SYNEPHRINE (10 mg, 15 mg, 20 mg) ON THE PULSE RATE IN SUBJECTS WITH COMMON COLD

(Fractional Units of t_0 Readings)

	t_0	t_{30}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0	t_{180}/t_0	t_{240}/t_0
Neo-Synephrine 10 mg	78.8	1.01	.98	.98	1.00	1.01	1.01
Placebo	78.5	.99	.98	.98	1.03	1.00	1.01
Analysis of Variance (s) (n = 15)	p>0.05 s=8.30	p>0.05 s=0.06	p>0.05 s=0.09	p>0.05 s=0.07	p>0.05 s=0.05	p>0.05 s=0.06	p>0.05 s=0.06
Neo-Synephrine 15 mg	76.9	.98	1.00	1.01	1.00	1.00	1.00
Placebo	76.0	1.01	.99	1.00	1.00	1.02	1.00
Analysis of Variance (s) (n = 16)	p>0.05 s=5.80	p>0.05 s=0.05	p>0.05 s=0.04	p>0.05 s=0.04	p>0.05 s=0.07	p>0.05 s=0.07	p>0.05 s=0.08
Neo-Synephrine 20 mg	77.2	1.01	.99	1.01	1.00	1.02	.99
Placebo	77.5	.97	.99	.96	1.04	1.02	1.02
Analysis of Variance (s) (n = 15)	p>0.05 s=5.75	p>0.05 s=0.08	p>0.05 s=0.06	p>0.05 s=0.05	p>0.05 s=0.06	p>0.05 s=0.07	p>0.05 s=0.08

Table IV

COMPARISON OF THE EFFECT OF ORAL NEO-SYNEPHRINE (10 mg, 15 mg, 20 mg) ON THE SYSTOLIC BLOOD PRESSURE IN SUBJECTS WITH COMMON COLD

(Fractional Units of t_0 Readings)

	t_0	t_{30}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0	t_{180}/t_0	t_{240}/t_0
Neo-Synephrine 10 mg	112	1.01	1.01	1.00	1.01	1.03	1.02
Placebo	114	.99	1.00	1.00	1.00	1.00	.99
Analysis of Variance (s) (n= 15)	p>0.05 s=4.46	p>0.05 s=0.03	p>0.05 s=0.02	p>0.05 s=0.04	p>0.05 s=0.03	p>0.05 s=0.05	p>0.05 s=0.03
Neo-Synephrine 15 mg	113	.99	.99	.98	.98	.97	.98
Placebo	115	.99	.98	.98	.98	1.00	.99
Analysis of Variance (s) (n = 16)	p>0.05 s=6.96	p>0.05 s=0.04	p>0.05 s=0.05	p>0.05 s=0.05	p>0.05 s=0.07	p>0.05 s=0.08	p>0.05 s=0.06
Neo-Synephrine 20 mg	112	.99	.98	1.00	.99	.99	.99
Placebo	110	1.00	1.01	1.02	1.01	1.02	1.01
Analysis of Variance (s) (n = 15)	p>0.05 s=5.16	p>0.05 s=0.03	p>0.05 s=0.04	p>0.05 s=0.04	p>0.05 s=0.04	p>0.05 s=0.08	p>0.05 s=0.04

Table V

COMPARISON OF THE EFFECT OF ORAL NEO-SYNEPHRINE (10 mg, 15 mg, 20 mg) ON THE DIASTOLIC BLOOD PRESSURE IN SUBJECTS WITH COMMON COLD

(Fractional Units of t_0 Readings)

	t_0	t_{30}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0	t_{180}/t_0	t_{240}/t_0
Neo-Synephrine 10 mg	74	1.00	1.01	1.04	1.03	1.00	1.02
Placebo	77	.98	.96	.98	1.00	.98	.97
Analysis of Variance (s) (n = 15)	p>0.05 s=7.32	p>0.05 s=0.08	p>0.05 s=0.07	p>0.05 s=0.06	p>0.05 s=0.07	p>0.05 s=0.07	p>0.05 s=0.09
Neo-Synephrine 15 mg	71	1.02	1.04	1.01	1.00	1.03	1.00
Placebo	74	1.01	.99	.99	1.01	.99	1.00
Analysis of Variance (s) (n = 16)	p>0.05 s=6.07	p>0.05 s=0.08	p>0.05 s=0.08	p>0.05 s=0.07	p>0.05 s=0.06	p>0.05 s=0.08	p>0.05 s=0.08
Neo-Synephrine 20 mg	72	1.01	1.02	1.01	1.00	1.02	1.02
Placebo	73	.99	.99	1.03	1.03	1.02	1.04
Analysis of Variance (s) (n = 15)	p>0.05 s=4.57	p>0.05 s=0.05	p>0.05 s=0.07	p>0.05 s=0.07	p>0.05 s=0.09	p>0.05 s=0.08	p>0.05 s=0.06

Objective Measurement Means*
Neo-Synephrine (10 mg)

Patient	Treatment	t_0**	t_{15}***	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}	t_{180}	t_{240}
1	Drug	30.8	0.99	1.00	0.86	0.77	0.72	0.65	0.67	0.65
	Placebo	41.3	1.00	1.03	0.99	0.93	0.89	0.91	1.04	1.04
3	Drug	25.9	1.05	0.96	0.86	0.85	0.99	0.94	1.00	1.15
	Placebo	27.2	1.01	0.85	0.79	0.71	0.62	0.55	0.42	0.36
7	Drug	33.3	1.18	0.96	1.07	0.92	0.97	0.91	0.86	0.87
	Placebo	23.9	1.29	1.09	1.11	1.10	0.80	0.52	0.54	0.68
10	Drug	27.1	0.98	1.01	0.89	0.76	0.79	0.69	0.51	0.30
	Placebo	27.0	1.03	1.03	1.01	1.00	1.02	1.04	0.99	0.99
12	Drug	38.4	0.99	0.96	0.95	0.83	0.86	0.68	0.53	0.44
	Placebo	38.8	1.02	0.95	0.89	0.90	0.77	0.83	0.89	0.85
17	Drug	48.4	1.01	0.98	1.00	1.01	1.01	1.01	1.01	0.99
	Placebo	46.8	0.99	0.97	0.97	0.97	0.76	0.50	0.44	0.25
24	Drug	42.2	1.04	1.09	1.11	0.90	0.79	0.83	0.62	0.50
	Placebo	35.8	1.03	1.01	1.02	1.00	1.02	0.83	0.59	0.64
26	Drug	23.8	0.68	0.73	0.67	0.62	0.62	0.62	0.56	0.48
	Placebo	12.6	1.04	0.85	0.79	0.70	0.66	0.55	0.53	0.49
27	Drug	23.6	0.90	0.95	0.91	0.87	0.87	0.85	0.72	0.48
	Placebo	16.4	0.80	0.81	0.80	0.89	0.90	0.81	0.77	0.66
30	Drug	18.1	1.01	1.07	0.93	0.97	0.99	0.76	0.76	0.76
	Placebo	21.0	1.10	0.96	0.76	0.71	0.65	0.69	0.61	0.63
32	Drug	29.7	0.98	0.87	0.89	0.96	0.97	0.87	0.94	0.84
	Placebo	31.0	0.85	0.75	0.71	0.66	0.69	0.60	0.58	0.47
34	Drug	15.1	0.90	0.90	0.93	0.82	0.92	0.76	0.79	0.73
	Placebo	18.8	0.78	0.71	0.65	0.66	0.68	0.58	0.49	0.45
37	Drug	33.6	0.80	0.89	0.90	0.80	0.78	0.75	0.77	0.76
	Placebo	20.5	0.84	1.07	1.36	1.45	1.45	1.51	1.53	1.53
39	Drug	16.7	0.94	0.82	0.72	0.70	0.66	0.64	0.57	0.54
	Placebo	20.0	0.88	0.87	0.81	0.81	0.82	0.79	0.78	0.67
44	Drug	14.0	0.97	0.94	0.87	0.92	0.85	1.07	0.93	1.24
	Placebo	19.9	0.80	0.90	0.83	1.24	0.98	0.99	0.81	0.65

*Each number represents the mean of 5 measurements on both right and left nostrils.

t_0: premedication reading (units) *t_{15}, etc.: mean as % of t_0

Objective Measurement Means
Neo-Synephrine (15 mg)

Patient	Treatment	t_0**	t_{15}***	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}	t_{180}	t_{240}
2	Drug	22.4	0.91	0.82	0.73	0.82	0.78	0.75	0.60	0.44
	Placebo	20.6	0.94	1.01	0.95	0.94	0.91	0.89	0.69	0.72
6	Drug	47.4	0.97	0.88	0.79	0.78	0.78	0.75	0.79	0.74
	Placebo	44.0	1.04	0.94	1.06	0.92	0.65	0.54	0.52	0.41
11	Drug	40.9	1.02	0.90	0.89	0.85	0.81	0.68	0.64	0.47
	Placebo	39.0	3.53	0.91	0.91	0.88	0.94	0.97	0.98	0.93
15	Drug	28.7	1.03	1.02	1.02	0.90	0.77	0.63	0.48	0.27
	Placebo	31.9	0.99	0.99	0.99	0.96	0.94	0.95	0.98	0.94
16	Drug	31.5	0.98	0.96	0.96	0.95	1.04	1.05	0.99	1.04
	Placebo	35.7	0.96	0.92	0.84	0.64	0.58	0.46	0.29	0.15
20	Drug	31.4	1.01	1.00	0.98	0.95	0.96	0.72	0.61	0.46
	Placebo	26.4	1.09	1.09	1.13	1.11	1.10	1.07	0.92	0.95
21	Drug	20.8	1.02	1.01	1.02	0.99	0.94	0.75	0.32	0.19
	Placebo	20.2	0.98	1.00	0.98	1.01	0.99	1.02	0.99	1.02
25	Drug	41.3	0.78	0.78	0.78	0.77	0.59	0.62	0.60	0.59
	Placebo	35.0	1.07	1.05	1.07	0.92	0.87	0.87	0.54	0.62
29	Drug	13.0	1.08	1.11	1.04	0.83	0.77	0.74	0.68	0.70
	Placebo	17.9	0.79	0.69	0.66	0.77	0.77	0.67	0.66	0.57
35	Drug	14.4	0.96	0.94	0.88	0.80	0.74	0.61	0.59	0.55
	Placebo	12.3	1.05	1.00	0.96	0.86	0.82	0.87	0.85	0.65
40	Drug	14.0	0.95	0.85	0.79	0.80	0.76	0.59	0.56	0.50
	Placebo	12.9	0.96	0.93	0.95	0.95	0.97	0.91	0.77	0.81
41	Drug	26.1	1.04	1.01	0.99	0.95	1.06	1.01	0.90	0.78
	Placebo	27.9	1.03	1.08	1.07	1.12	1.07	1.03	0.92	0.82
43	Drug	14.8	0.90	0.85	0.87	0.77	0.72	0.65	0.66	0.58
	Placebo	15.1	1.01	0.90	0.85	0.86	0.78	0.70	0.68	0.79
45	Drug	16.7	0.92	0.89	0.90	0.91	0.78	0.68	0.73	0.70
	Placebo	20.9	0.92	0.87	0.91	0.93	0.91	0.66	0.62	0.65
46	Drug	10.2	1.01	0.98	0.95	0.88	0.90	0.83	0.84	0.54
	Placebo	11.7	0.94	0.96	0.95	0.84	0.81	0.75	0.73	0.68
48	Drug	25.6	0.92	0.87	0.80	0.83	0.87	0.78	0.92	0.73
	Placebo	19.6	1.04	1.02	1.01	0.97	0.90	0.89	0.81	0.46

*Each number represents the mean of 5 measurements on both right and left nostrils.

t_0: premedication reading (units) *t_{15}, etc.: mean as % of t_0

APPENDIX

Objective Measurement Means*
Neo-Synephrine (20 mg)

Patient	Treatment	t_0**	t_{15}***	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}	t_{180}	t_{240}
4	Drug	22.2	0.96	1.00	1.04	1.03	1.00	0.98	1.02	0.94
	Placebo	24.5	0.91	0.98	0.95	1.06	0.99	0.82	0.51	0.42
5	Drug	30.8	0.93	0.91	0.98	0.85	0.73	0.70	0.90	0.82
	Placebo	30.1	0.97	0.98	0.99	0.89	1.01	0.96	0.94	0.75
8	Drug	26.3	1.18	1.15	1.16	0.84	1.02	1.12	1.18	1.08
	Placebo	30.9	1.16	1.18	1.28	1.00	0.88	0.71	0.46	0.33
9	Drug	29.7	1.06	1.03	1.18	1.12	1.26	1.16	1.19	1.14
	Placebo	24.6	0.99	0.83	0.95	0.75	0.62	0.45	0.28	0.18
13	Drug	31.1	1.06	1.07	1.05	1.06	1.01	0.72	0.59	0.47
	Placebo	30.8	0.98	0.98	1.01	0.95	0.98	1.00	1.05	1.04
14	Drug	33.9	0.97	0.96	0.90	0.84	0.68	0.54	0.39	0.24
	Placebo	29.8	1.02	1.22	1.22	1.01	1.06	1.11	1.11	1.12
18	Drug	26.2	0.97	0.99	0.93	0.94	0.95	0.97	0.96	0.92
	Placebo	28.0	0.96	0.96	0.93	0.82	0.76	0.63	0.49	0.22
19	Drug	24.0	1.01	1.00	1.02	1.01	1.02	1.01	0.97	0.97
	Placebo	25.7	1.04	1.02	1.00	0.93	0.84	0.68	0.33	0.23
22	Drug	25.7	1.04	1.01	1.04	0.91	0.92	0.78	0.54	0.50
	Placebo	25.0	0.98	0.98	0.97	0.97	0.95	0.96	0.92	0.94
23	Drug	33.6	0.99	1.00	1.07	1.00	0.95	0.90	0.67	0.53
	Placebo	32.7	1.03	1.03	1.07	1.19	1.18	1.23	1.03	0.67
28	Drug	12.5	0.91	0.87	0.92	0.91	0.87	0.86	0.69	0.68
	Placebo	12.5	1.16	1.21	1.06	1.25	1.21	0.99	1.05	0.78
36	Drug	15.1	1.02	0.89	0.78	0.69	0.75	0.62	0.61	0.52
	Placebo	18.4	0.87	0.76	0.66	0.75	0.81	0.76	0.73	0.71
38	Drug	11.9	1.27	1.26	1.13	1.05	1.06	0.82	0.82	0.78
	Placebo	21.3	0.84	0.79	0.79	0.86	0.88	0.72	0.74	0.72
42	Drug	14.3	0.92	0.86	0.83	0.74	0.75	0.77	0.71	0.70
	Placebo	13.1	0.91	0.91	0.85	0.89	0.85	0.76	0.69	0.63
47	Drug	15.8	0.78	0.71	0.77	0.74	0.77	0.72	0.62	0.63
	Placebo	14.4	0.91	0.89	0.83	0.84	0.87	0.81	0.75	0.65

*Each number represents the mean of 5 measurements on both right and left nostrils.

t_0: premedication reading (units) *t_{15}, etc.: mean as % of t_0

REFERENCE 9

STERLING-WINTHROP RESEARCH INSTITUTE

MEDICAL RESEARCH DIVISION

May 18, 1970

Ref # 24

To: Dr. Blackmore

From: N. A. Hulme

Re: Oral Neo-Synephrine - Cintest Study No. 3

As part of the continuing program for the evaluation of the nasal decongestant activity of orally administered Neo-Synephrine, a third study with the Cintest group in Cincinnati was approved October 27, 1969, to be carried out during the 1969-70 winter cold season. This decision was based, in part, on the successful completion of the first study (Hulme to Blackmore 4-10-69) and the anticipated successful completion of the second. Although, subsequent analyses of the latter results failed to show a positive drug effect (Hulme to Blackmore 1-23-70).

The Neo-Synephrine dosages used in this study were those recommended at the May 19, 1969, Medical Research Conference.

Protocol and Methodology

A total of 48 subjects with head colds and having confirmed nasal congestion on two consecutive days participated in the study. Evaluation of the degree of nasal congestion was made by measuring the relative resistance to a constant flow of air passing through the nasal passageway by a modification of the Butler-Ivy procedure (Blanchard et al E.E.N.T. Monthly 43, 76-82, 1964).

The subjects were assigned coded drugs on a double-blind randomized basis. The randomization was designed so that half the subjects in each dose category received placebo on the first day and active medication on the second day. The reversed sequence occurred with the other subjects. The following table gives the number of subjects receiving each of the drugs.

No. of Subjects	Neo-Synephrine vs. Placebo
16	10 mg
16	15 mg
16	25 mg

All drugs were supplied in identical capsules and packaged in individual preassigned envelopes labeled by code number and subject number.

Objective measurements of airflow resistance were carried out by obtaining five consecutive readings for each nostril at 0, 15 and 30 minutes before medication and 15, 30, 45, 60, 90 and 120 minute intervals following medication. The ten readings from both nostrils were combined and the arithmetic means employed for further calculations and analysis.

Subjective impressions of changes in nasal congestion were obtained by having each subject describe his congestion at the time each set of airflow measurements were made. These were classified as being closest to one of the following conditions:

Degree of Congestion
Nose feels clear
Almost clear
Stuffy
Very stuffy
Completely blocked

A shift of one degree of congestion from the premedication state was graded as plus or minus 1, a shift in two degrees as plus or minus 2, etc. The sums of the change at each time interval were recorded for each subject. The median change for all subjects on each active medication dosage was compared to the same subject's placebo scores for significance of the difference.

Pulse and sitting blood pressure readings were obtained on each subject at 30, 15 and 0 minutes before medication and at 30. 60, 90 and 120 minutes following medication. The readings from each medication group were combined and the arithmetic means employed for further calculations and analysis. This provided comparisons between active medication and placebo for diastolic pressure, systolic pressure and pulse rate.

Results and Discussion

The air resistance values for each subject (see Apprendix) were used to calculate arithmetic differences between premedication and postmedication results at the indicated specific time intervals. These data were analyzed by the Biostatistical Department for significance between the placebo and medication readings. The mean values and the degree of significance at each of the dosages are given in Table I. The data for each dosage: placebo pair have been plotted as graphs in Figures 1 to 3.

It is apparent from Figure 1 that placebo and 10 mg Neo-Synephrine were indistinguishable. In Figures 2 and 3 it can be seen that even though an apparent separation occurred between placebo and Neo-Synephrine 15 mg and 25 mg that the magnitude of the difference was quite small. The results of the analysis bear this out and indicate only a questionable statistically significant separation occurring at the 30 minute time interval with the 15 mg dose.

An analysis of the subjective impressions of changes in degree of nasal congestion was carried out. The mean values and the degree of significance for each drug dose are presented in Table II. The results show that a statistically significant number of subjects (at the 5% level) receiving the 15 mg dose of Neo-Synephrine felt a greater degree of relief than when on placebo. Subjects receiving either 10 mg or 25 mg Neo-Synephrine could not distinguish between placebo and active drug.

Tables III, IV and V provide comparative data on changes in pulse rate, systolic blood pressure and diastolic blood pressure, respectively, for subjects receiving the three doses of Neo-Synephrine and placebo.

Analysis of the pulse rate data revealed that a statistically significant increase occurred in subjects receiving the 15 mg dose at the 90 minute reading. No other statistically significant changes occurred. Inasmuch as the direction of change is opposite to that expected of a true drug effect its meaning is unclear.

Statistically significant changes occurred in the systolic blood pressure at the 60 minute reading on both the 15 mg dose and 25 mg dose. The latter was a decrease and consequently of questionable significance. The former represents an increase of less than 3 mm Hg. A change of this magnitude is clearly not clinically meaningful.

Statistically significant decreases in diastolic pressure occurred at the 90 and 120 minute readings with the 25 mg dose. Inasmuch as these were in a direction opposite to that expected from a true drug effect their meaning is open to question.

Summary

The objective results indicate a very minimal drug effect in terms of measurable decongestant changes. Subjective changes also of a very minimal degree correlating with the objective changes were observed. The minor cardiovascular changes which were noted were without clinical significance. The overall impression gathered from this study is one of a threshold decongestant effect without clinical importance.

N. A. Hulme

bjc

cc: Dr. Wessinger
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Table I

COMPARISON OF THE NASAL DECONGESTANT EFFECT OF ORAL NEO-SYNEPHRINE (10 mg, 15 mg, 20 mg) VERSUS PLACEBO IN SUBJECTS WITH COMMON COLD

Objective Measurements (fractional units)

	t_0	t_{15}/t_0	t_{30}/t_0	t_{45}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0
Neo-Synephrine 10 mg	21.3	.98	.97	.97	.93	.88	.86
Placebo	21.3	1.01	.97	.95	.91	.86	.78
Analysis of Variance (s) (n = 15)	p>0.05 s=5.29	p>0.05 s=0.09	p>0.05 s=0.16	p>0.05 s=0.17	p>0.05 s=0.20	p>0.05 s=0.23	p>0.05 s=0.23
Neo-Synephrine 15 mg	24.0	.96	.88	.84	.82	.78	.72
Placebo	24.4	.98	.99	.94	.89	.80	.79
Analysis of Variance (s) (n = 16)	p>0.05 s=2.97	p>0.05 s=0.09	p=0.10 s=0.15	p>0.05 s=0.16	p>0.05 s=0.20	p>0.05 s=0.17	p>0.05 s=0.25
Neo-Synephrine 25 mg	19.2	.95	.90	.85	.81	.75	.73
Placebo	17.7	.99	.94	.93	.92	.85	.79
Analysis of Variance (s) (n = 16)	p>0.05 s=2.47	p>0.05 s=0.09	p>0.05 s=0.11	p>0.05 s=0.16	p=0.10 s=0.17	p>0.05 s=0.19	p>0.05 s=0.22

Table II

COMPARISON OF THE NASAL DECONGESTANT EFFECT OF ORAL NEO-SYNEPHRINE (10 mg, 15 mg, 25 mg) VERSUS PLACEBO IN SUBJECTS WITH COMMON COLD

Subjective Impression Differences

	Median Differences	Analysis of Variance	Standard Deviation	Number of Subjects
Neo-Synephrine 10 mg	-2.27	p>0.05	2.41	15
Placebo	-2.00			
Neo-Synephrine 20 mg	-3.87	p=0.05	4.33	16
Placebo	-0.25			
Neo-Synephrine 25 mg	-2.38	p>0.05	3.59	16
Placebo	-2.94			

Table III

COMPARISON OF THE EFFECT OF ORAL NEO-SYNEPHRINE (10 mg, 15 mg, 25 mg) ON THE PULSE RATE IN SUBJECTS WITH COMMON COLD

(Fractional Units of t_0 Readings)

	t_0	t_{30}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0
Neo-Synephrine 10 mg	81.9	1.00	.92	1.00	1.00
Placebo	81.1	.97	.97	.98	.99
Analysis of Variance (s) (n = 15)	p>0.05 s=5.95	p>0.05 s=0.05	p>0.05 s=0.06	p>0.05 s=0.06	p>0.05 s=0.07
Neo-Synephrine 15 mg	76.6	1.02	1.04	1.05	1.04
Placebo	77.0	1.01	1.02	1.01	1.02
Analysis of Variance (s) (n = 16)	p>0.05 s=3.94	p>0.05 s=0.06	p>0.05 s=0.05	p=0.01 s=0.03	p>0.05 s=0.04
Neo-Synephrine 25 mg	80.3	1.00	1.02	1.01	1.01
Placebo	77.4	1.00	1.01	1.02	1.01
Analysis of Variance (s) (n = 16)	p>0.05 s=5.09	p>0.05 s=0.05	p>0.05 s=0.05	p>0.05 s=0.04	p>0.05 s=0.04

Table IV

COMPARISON OF THE EFFECT OF ORAL NEO-SYNEPHRINE (10 mg, 15 mg, 25 mg) ON THE SYSTOLIC BLOOD PRESSURE IN SUBJECTS WITH COMMON COLD

(Fractional Units of t_0 Readings)

	t_0	t_{30}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0
Neo-Synephrine 10 mg	110	1.01	1.01	1.00	1.01
Placebo	111	1.00	.99	.98	.99
Analysis of Variance (s) (n = 15)	p>0.05 s=3.57	p>0.05 s=0.23	p>0.05 s=0.03	p>0.05 s=0.04	p>0.05 s=0.05
Neo-Synephrine 15 mg	110	1.00	.99	1.00	1.00
Placebo	112	1.00	.97	.98	.98
Analysis of Variance (s) (n = 16)	p>0.05 s=3.99	p>0.05 s=0.03	p=0.01 s=0.02	p>0.05 s=0.04	p>0.05 s=0.05
Neo-Synephrine 25 mg	108	1.00	.99	1.01	1.01
Placebo	108	1.01	1.01	1.04	1.06
Analysis of Variance (s) (n = 16)	p>0.05 s=5.17	p>0.05 s=0.04	p=0.05 s=0.03	p>0.05 s=0.05	p>0.05 s=0.05

Table V

COMPARISON OF THE EFFECT OF ORAL NEO-SYNEPHRINE (10 mg, 15 mg, 25 mg) ON THE DIASTOLIC BLOOD PRESSURE IN SUBJECTS WITH COMMON COLD

(Fractional Units of t_0 Readings)

	t_0	t_{30}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0
Neo-Synephrine 10 mg	70.3	.99	1.00	.98	.99
Placebo	68.9	1.01	1.02	1.00	1.00
Analysis of Variance (s) (n = 15)	p>0.05 s=4.95	p>0.05 s=0.06	p>0.05 s=0.07	p>0.05 s=0.06	p>0.05 s=0.07
Neo-Synephrine 15 mg	67.3	1.01	.97	1.02	1.01
Placebo	67.8	.99	.99	1.00	.99
Analysis of Variance (s) (n = 16)	p>0.05 s=5.48	p>0.05 s=0.04	p>0.05 s=0.06	p>0.05 s=0.06	p>0.05 s=0.10
Neo-Synephrine 25 mg	69.9	.99	.99	.99	1.00
Placebo	66.5	1.03	1.02	1.07	1.07
Analysis of Variance (s) (n = 16)	p>0.05 s=4.64	p>0.05 s=0.06	p>0.05 s=0.05	p=0.05 s=0.09	p=0.05 s=0.07

Figure 1

Comparison of the Nasal Decongestant Effect of Neo-Synephrine 10 mg. and Placebo in 15 Subjects with Common Cold

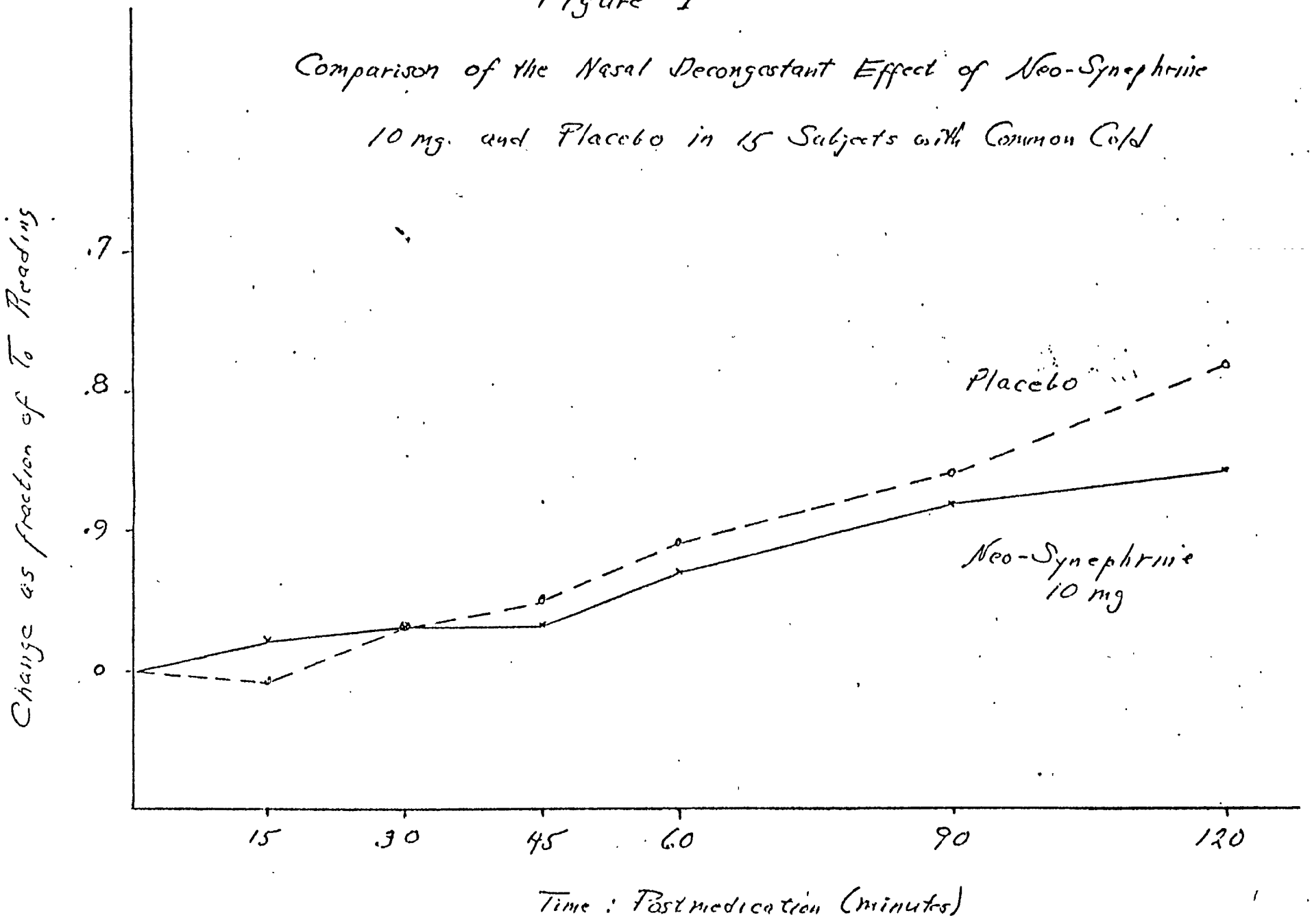


Figure 2

Comparison of the Nasal Decongestant Effect of Neo-Synephrine 15 mg. and Placebo in 16 Subjects with Common Cold

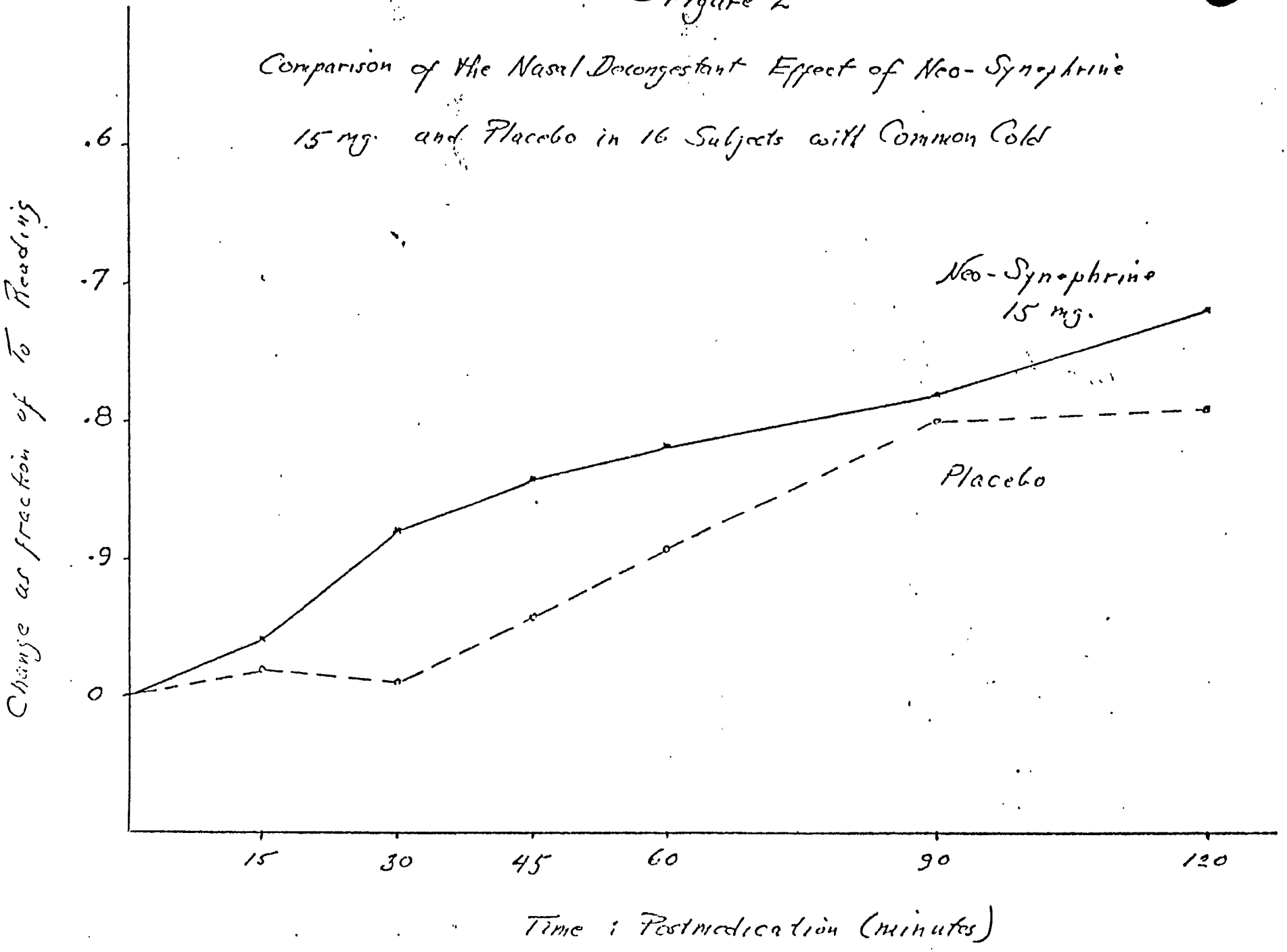
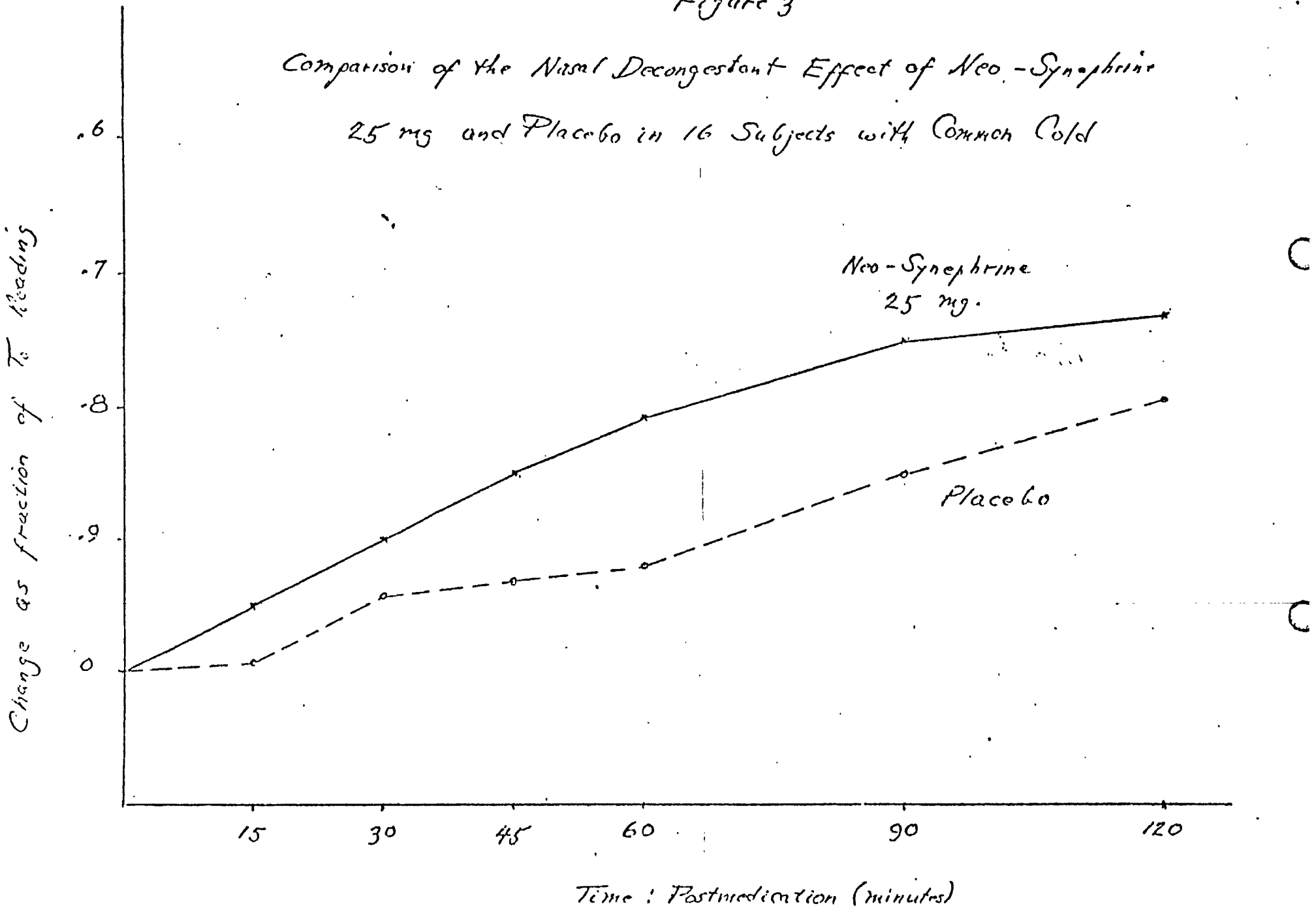


Figure 3

Comparison of the Nasal Decongestant Effect of Neo-Synephrine 25 mg and Placebo in 16 Subjects with Common Cold



Objective Measurement Means
Neo-Synephrine (10 mg)

Patient	Treatment	t_0**	t_{15}***	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}
1	Drug	19.2	0.90	0.94	0.95	1.14	0.80	0.78
	Placebo	28.7	0.89	0.90	0.91	0.90	0.78	0.78
10	Drug	11.5	1.10	1.13	0.95	0.90	0.84	0.82
	Placebo	11.3	1.02	1.11	1.05	1.07	1.11	0.81
13	Drug	34.0	0.91	0.69	0.73	0.65	0.62	0.61
	Placebo	17.6	1.18	1.26	1.18	1.18	1.06	0.80
15	Drug	13.7	0.95	0.88	0.88	0.82	0.73	0.71
	Placebo	14.2	1.05	1.04	0.99	0.97	0.93	0.95
21	Drug	24.4	0.94	0.91	0.93	0.72	0.66	0.60
	Placebo	15.0	1.05	1.01	0.97	0.98	1.02	1.01
22	Drug	16.4	1.14	1.22	1.18	0.91	0.87	0.88
	Placebo	19.5	0.94	0.86	0.84	0.86	0.74	0.78
25	Drug	21.2	0.85	0.87	0.99	0.83	0.72	0.74
	Placebo	24.9	0.99	1.02	1.08	1.08	1.10	0.98
27	Drug	19.6	0.99	1.19	1.29	1.41	1.44	1.44
	Placebo	25.4	1.09	0.83	0.80	0.78	0.66	0.55
29	Drug	40.6	1.01	1.01	0.89	0.94	0.99	0.91
	Placebo	32.6	0.99	1.06	1.15	0.88	0.91	0.90
30	Drug	29.4	1.06	0.94	0.94	0.88	0.83	0.77
	Placebo	29.5	1.13	1.00	0.92	0.87	0.88	0.80
32	Drug	19.0	1.02	0.83	0.86	0.92	0.87	0.85
	Placebo	15.6	0.97	0.86	0.81	0.76	0.65	0.62
34	Drug	13.4	0.91	0.95	0.90	0.83	0.80	0.78
	Placebo	21.1	0.95	0.97	0.97	0.90	0.73	0.67
35	Drug	22.3	1.09	1.02	0.96	0.89	0.96	1.00
	Placebo	19.6	1.05	0.91	0.92	0.88	0.80	0.74
43	Drug	15.7	0.99	0.96	0.97	0.96	0.95	0.95
	Placebo	27.3	0.88	0.72	0.65	0.63	0.58	0.50
46	Drug	16.9	1.00	1.02	1.00	0.94	0.87	0.83
	Placebo	18.5	1.13	1.06	1.06	1.14	1.08	1.14

*Each number represents the mean of 5 measurements on both right and left nostrils.

t_0: premedication reading (units) *t_{15}, etc.: mean as % of t_0

Objective Measurement Means*
Neo-Synephrine (15 mg)

Patient	Treatment	t_0**	t_{15}***	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}
3	Drug	17.0	0.83	0.75	0.75	0.71	0.86	0.88
	Placebo	17.4	0.96	0.85	0.83	0.94	0.64	0.55
4	Drug	16.4	0.84	0.83	0.84	0.76	0.73	0.71
	Placebo	14.2	0.95	1.00	0.99	0.88	0.82	0.84
7	Drug	11.5	0.94	0.96	0.88	0.77	0.68	0.66
	Placebo	11.5	0.90	0.89	0.80	0.74	0.59	0.50
8	Drug	27.1	0.99	1.05	1.00	1.04	1.05	1.08
	Placebo	32.6	0.97	1.05	0.90	0.91	0.86	0.60
11	Drug	39.3	0.99	0.80	0.79	0.73	0.75	0.64
	Placebo	35.6	1.01	1.06	1.10	1.07	0.90	0.94
14	Drug	17.0	0.94	0.89	0.78	0.71	0.65	0.55
	Placebo	16.7	1.16	1.07	1.01	0.93	0.82	0.89
16	Drug	24.9	1.06	0.84	0.88	0.91	1.00	0.98
	Placebo	29.7	0.77	0.65	0.52	0.43	0.46	0.36
17	Drug	24.5	0.94	0.60	0.63	0.58	0.52	0.42
	Placebo	25.1	0.86	1.21	1.23	1.25	0.78	1.07
19	Drug	24.5	0.85	0.73	0.72	0.71	0.73	0.67
	Placebo	25.2	1.03	1.01	0.87	0.85	0.83	0.81
24	Drug	34.4	0.98	0.98	0.93	0.98	0.82	0.76
	Placebo	37.8	0.92	0.81	0.80	0.66	0.68	0.61
28	Drug	28.4	1.04	1.15	0.96	0.94	0.75	0.48
	Placebo	35.9	0.97	1.06	1.09	0.74	0.69	0.69
31	Drug	21.0	1.07	1.02	0.99	1.02	1.06	1.02
	Placebo	24.8	1.14	0.84	0.80	0.79	0.77	0.75
38	Drug	11.5	0.98	0.92	0.87	0.83	0.83	0.79
	Placebo	12.1	1.00	1.02	1.01	1.00	0.98	1.07
39	Drug	37.1	0.95	0.85	0.79	0.76	0.73	0.66
	Placebo	35.2	1.07	1.09	1.07	1.03	1.05	1.06
41	Drug	27.1	0.99	0.89	0.92	0.84	0.82	0.65
	Placebo	22.1	1.02	1.17	1.02	0.99	0.96	0.94
44	Drug	23.5	0.97	0.82	0.76	0.77	0.62	0.55
	Placebo	14.4	1.02	1.04	1.06	1.03	0.96	0.93

*Each number represents the mean of 5 measurements on both right and left nostrils.

t_0: premedication reading (units) *t_{15}, etc.: mean as % of t_0

Objective Measurement Means*
Neo-Synephrine (25 mg)

Patient	Treatment	t_0**	t_{15}***	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}
2	Drug	16.9	0.93	0.90	0.94	0.85	0.60	0.55
	Placebo	13.1	1.12	1.08	1.08	1.00	0.96	0.86
5	Drug	10.7	0.90	0.90	0.84	0.78	0.58	0.51
	Placebo	11.7	0.91	0.90	0.92	0.80	0.75	0.72
6	Drug	11.8	1.14	1.11	1.10	1.15	1.01	1.11
	Placebo	14.5	0.99	0.99	0.96	1.12	0.99	0.83
9	Drug	26.5	0.80	0.78	0.76	0.76	0.85	0.83
	Placebo	21.5	0.68	0.59	0.56	0.62	0.54	0.47
12	Drug	17.0	0.85	0.78	0.73	0.71	0.64	0.67
	Placebo	11.4	0.91	0.95	1.04	0.99	0.81	0.74
18	Drug	20.4	0.81	0.90	0.74	0.58	0.63	0.58
	Placebo	15.2	1.11	1.05	1.20	1.18	1.18	1.11
20	Drug	20.1	1.05	1.00	0.95	0.94	0.92	0.83
	Placebo	14.9	1.01	1.05	1.00	1.01	0.89	0.80
26	Drug	17.9	0.99	1.01	0.97	0.91	0.86	0.89
	Placebo	18.9	0.93	0.84	0.78	0.72	0.72	0.65
33	Drug	24.8	0.96	0.85	0.82	0.76	0.69	0.61
	Placebo	22.9	0.96	0.96	0.93	0.90	0.91	0.88
36	Drug	20.8	0.90	0.84	0.75	0.75	0.74	0.78
	Placebo	17.9	1.13	1.13	1.10	1.06	0.90	0.72
37	Drug	17.7	0.98	0.83	0.81	0.79	0.71	0.67
	Placebo	15.7	0.99	0.98	0.97	0.92	0.98	0.96
40	Drug	18.4	0.96	0.98	0.99	0.96	0.95	0.92
	Placebo	18.0	0.99	0.90	0.85	0.83	0.81	0.77
42	Drug	29.8	0.95	0.71	0.57	0.57	0.44	0.44
	Placebo	26.3	0.99	0.96	1.00	1.07	0.98	0.98
45	Drug	20.8	1.02	1.02	0.69	0.67	0.57	0.58
	Placebo	27.9	0.99	0.82	0.69	0.67	0.39	0.38
47	Drug	19.9	0.91	0.83	0.82	0.72	0.69	0.64
	Placebo	18.1	1.02	0.94	0.97	0.97	1.01	0.99
48	Drug	13.6	0.99	1.01	1.01	1.04	1.07	1.06
	Placebo	15.1	1.05	0.89	0.84	0.80	0.77	0.70

*Each number represents the mean of 5 measurements on both right and left nostrils.

t_0: premedication reading (units) *t_{15}, etc.: mean as % of t_0

REFERENCE 10

June 1975 Final Report: Evaluation of the effectiveness of Phenylephrine HCl tablets (5 mg) in the relief of upper respiratory congestion and symptoms associated with the common cold in a 200 patient study conducted for Whitehall Laboratories (OTC Volume 040288B)

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Appendix

BIO-EVALUATION, INC. 576 FIFTH AVE., NEW YORK, N.Y. 10036 (212) 575-7816

BEI 1025 June 1975

Final Report:

Evaluation of the effectiveness of phenylephrine HCl tablets (5 mg) in the relief of upper respiratory congestion and symptoms associated with the common cold in a 200 patient study conducted for Whitehall Laboratories.

Study Objective:

1. To compare by objective measurements (electronic posterior rhinometry) the decongestant effectiveness of phenylephrine HCl tablets (5 mg) vs. placebo tablets in patients having upper respiratory congestion associated with common cold when the measurements are made at 0, 15, 30, 60, and 120 minutes following oral administration of two tablets as a single dose of the cited contrasting treatments.

2. To concomitantly compare by subjective evaluation severity of symptoms involving stuffy nose, runny nose, sneezing, itching (eyes, nose), coughing, and muscle ache the decongestant effectiveness of the orally administered treatments observing the responses at the same times and in the same patients described in Objective 1.

3. After taking the first dose of treatments (2 tablets) and making the objective and subjective measurements described in Objectives 1 and 2, to discontinue with the objective measurements and continue with the subjective evaluation of active vs. placebo treatments by continuing with the respective 2 tablet treatments for the 2nd, 3rd, and 4th doses taken at 4 hour intervals and making the subsequent subjective evaluations at 4, 4½, 5½, 8, 8½, 12, and 12½ hours relative to the time the first dose of 2 tablets was given.

Conduct of Study

The study was conducted in compliance with the protocol titled: Objective and Subjective Evaluation of Phenylephrine HCl (5 mg) vs. Placebo Tablets. November 14, 1974, which was submitted by BEI and approved by Whitehall Laboratories.

Raw Data

The raw data consists of about 500 pages of case report forms completed as designated in the protocol and photographs of the oscilloscope traces. The raw data were submitted by BEI to Whitehall Laboratories on May 22, 1975.

The raw data for BEI 1025a are on Forms 4 and 5 and for BEI 1025b on Form 3.

Compilation of Raw Data

Accompanying this report is a compilation of the raw data consisting of 4 volumes each containing approximately 90 pages. The volumes are titled:

Volume 1. Compilation of Raw Data for Objective-Subjective Placebo Controlled Study Involving Phenylephrine HCl Tablets (5 mg)
Objective Study: BEI 1025a Group 1 Placebo

Volume 2. Compilation of Raw Data for Objective-Subjective Placebo Controlled Study Involving Phenylephrine HCl Tablets (5 mg)
Objective Study: BEI 1025a Group 2 Active

Volume 3. Compilation of Raw Data for Objective-Subjective Placebo Controlled Study Involving Phenylephrine HCl Tablets (5 mg)
Subjective Study: BEI 1025b Group 1 Placebo

Volume 4. Compilation of Raw Data for Objective-Subjective Placebo Controlled Study Involving Phenylephrine HCl Tablets (5 mg)
Subjective Study: BEI 1025b Group 2 Active

Summary

The safety and effectiveness of phenylephrine HCl 5 mg tablets, taken at the rate of 2 tablets every 4 hours for 12 hours for the relief of nasal congestion and the symptoms associated with the common cold, was evaluated in a 200 volunteer patient doubleblind placebo-controlled clinical investigation.

In 50 of the patients, nasal airway resistance measurements were made by electronic posterior rhinometry for the first two hours after treatment and subjective observations were made concurrently by the

Summary, contd.

patients of the degree of relief from stuffy nose, runny nose, sneezing, itching (eyes, nose), coughing, and muscle ache over a 12.5 hour period of observation.

In 150 of the patients, subjective observations only were made of the degree of relief from the indicated symptoms over a 12.5 hour period.

The 50 patient and 150 patient clinical investigations were conducted concurrently.

The data clearly show that phenylephrine HCl 5 mg tablets were safe and effective in the relief of nasal congestion and the symptoms of sneezing, runny nose, and stuffy nose. (Fig. 2, page 18; Fig. 6, page 22; Table 8, page 27).

Phenylephrine HCl tablets 5 mg were no more effective than the placebo in coughing and muscle ache. (Fig. 4, page 23).

The effectiveness of phenylephrine HCl tablets 5 mg in relieving the symptoms of itching (eyes, nose) could not be determined since only 3.5% of the patient population studied had this symptom (Table 7, page 13).

The phenylephrine tablets reduced nasal airway resistance 11% from the base line level in 15 minutes; 21% in 30 minutes; 28% in 60 minutes, and 26% in 120 minutes (Table 3, page 9, and Fig. 2, page 18). The corresponding values for the placebo tablet were: an increase of 0.2% in 15 minutes; a reduction of 6% in 30 minutes; a reduction of 13% in 60 minutes, and an increase of 6% in 120 minutes (Table 2, page 8, and Fig. 2, page 18). All of the post treatment differences between phenylephrine HCl vs. placebo at corresponding times are statistically significant at $P \leqq 5\%$.

Cohen[1] and other investigators[2,3,4] have stated that patients are most likely to notice desirable medical or biological changes in their own condition when the tests improve by a minimum of 20%. The reduction in nasal airway resistance occurring 30, 60, and 120 minutes after phenylephrine administration fell within the latter category.

Summary, contd.

The areas under the 0 to 12.5 hour rank sum curves derived from the subjective observations following phenylephrine HCl and placebo tablets administration, show that the order of effectiveness starting with the largest effect was: sneezing, 115% more effective than the placebo; runny nose, 85% more effective; and, stuffy nose, 58% more effective. With the exception of the 0 and ¼ hour rank sum values, the difference between phenylephrine HCl vs. the placebo for all the subsequent observations are statistically significant at $P < 5\%$. (Fig. 5, page 22)

The mean systolic blood pressure of the phenylephrine treated group was always higher (mean 1.3 mm Hg higher; range 0.2 to 1.4) than that of the placebo group. The mean diastolic blood pressure of the phenylephrine group, with one exception, was always lower (mean 0.56 mm Hg lower, range -0.2 to 0.6) than that of the placebo group. These differences are not statistically significant at the 5% level. (Fig. 8, page 26)

The patients' and the investigator's evaluation of the overall degree of the patients' subjective degree of relief from cold symptoms were in agreement as to the judgement that phenylephrine HCl tablets were more effective than the placebo tablets and as to the magnitude of the degree of relief obtained with phenylephrine tablets. (Fig. 7, page 25)

The data suggest that there was no significant different in the kind and number of side effects in the test and placebo groups. Of the 100 patients in the placebo group, 11 reported side effects; in the test group, 8. The following side effects were common to both groups: Dizzy (placebo, 3 patients; test, 1 patient); Felt warm (placebo, 1, test, 3). Only the placebo group reported the following side effects: Dizzy + Flushing, 1; Dry mouth, 3; Headache, 1; Nausea, 2. Only the test group reported: Extrasystoles, 1; Flush, 1; Nasal Dryness, 1; Slightly shaky, 1. (Table 8, page 27)

Results and Discussion

The organization of the section Results and Discussion is dictated by the fact that the study consists of 3 parts designated as:

- Objective-Subjective Study BEI 1025a (a total of 50 patients).
- Subjective Study BEI 1025b (a total of 150 patients).
- Objective-Subjective Study BEI 1025a + Subjective Study BEI 1025b (a total of 200 patients).

As the designations imply, in the Objective-Subjective Study the patients relief of upper respiratory congestion due to common cold was evaluated by both objective and subjective observations following the administration of the randomly doubleblind assignment of the patients to the active and placebo treatments. In the Subjective Study, only subjective observations were made of the response to the treatments. In the Objective-Subjective Study + Subjective Study, the subjective data from each study are pooled in evaluating the response to the treatments.

In evaluating the results of each of the 3 parts, it is first necessary to determine whether or not there was comparableness of the pertinent variables age, weight, height, race, sex, and initial presenting cold symptoms. Hence we first consider whether or not there was comparableness of the pertinent variables in each of the 3 parts of the study and then consider whether or not the differences in response between the test and control groups were medically and statistically significant.

Comparableness of the test and control groups

Objective-Subjective Study BEI 1025a

Inspection of Table 1 (page 6) shows that in the test and control groups there was comparableness of the pertinent variables age, weight, height, race, sex, and initial presenting cold symptoms. However, the comparableness of the initial degree of severity of nasal congestion evaluated by subjective and objective observations needs further examination.

(continued on page 7)

BEI 1025a

Objective-Subjective Study

Table 1. Patient population parameters in the test and control groups. (Source of data: Table 3 in Compilation of Raw Data for Objective-Subjective Study, Volumes 1 and 2.)

			Age (yrs)	Wt (lbs)	Ht ft	Ht in	Race* White	Negro	Oriental	Indian	Filipino	Sex* Male	Female	Initial presenting symptoms & severity: symptoms* StufNo	RunNo	Sneez	TchnNo	Cough	MusAch	HdAche	Oral T	severity of nasal congestion* Mild	Mod	ModSevr	Sevr	VSevr
			(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)	(21)	(22)	(23)	(24)
Men	Placebo	Mean	40.7	171	5	7	13	0	0	0	0	13	0	13	13	13	1	12	11	10	99.4	0	9	3	1	0
		Range	13-71	140-220	5-6	1-0															98.0-100					
	Active	Mean	53.0	168	5	9	9	0	0	0	0	9	0	9	9	9	0	9	8	5	99.5	2	3	4	0	0
		Range	21-74	139-199	5-6	1-1															99-99.8					
Women	Placebo	Mean	52.9	156	5	3	12	0	0	0	0	0	12	12	12	12	0	11	8	4	98.5	5	7	0	0	0
		Range	38-75	112-268	5-5	0-6															98-100					
	Active	Mean	54.1	152	5	5	15	1	0	0	0	0	16	16	16	16	0	16	15	8	98.5	5	6	5	0	0
		Range	22-80	99-216	5-6	0-0															99-100					
Men + Women	Placebo	Mean	46.6	164	5	5	25	0	0	0	0	13	12	25	25	25	1	23	19	14	98.5	5	16	3	1	0
		Range	13-75	112-268	5-6	0-0															99-100					
	Active	Mean	53.7	157	5	4	24	1	0	0	0	9	16	25	25	25	0	25	23	13	98.5	7	9	9	0	0
		Range	21-80	99-216	5-6	0-1															99-100					

* The numbers in the table are the number of patients.

Results and Discussion, contd.

Comparableness of the test and control groups, contd.

Objective-Subjective Study BEI 1025a, contd.

Severity of initial nasal congestion

Subjective Observations

In Table 1 (page 6), there is a suggestion that the severity of nasal congestion in the placebo group was less than that in the test group. The contrasting groups (Men + Woman: test vs. placebo) are nearly balanced insofar as severe cases (1 for placebo vs. 0 for test); mild cases (5 for placebo vs. 7 for test) and moderate + moderately severe cases (19 for placebo vs. 18 for test group). However, they are disproportionate for moderate cases (16 for placebo vs. 9 for test), and moderately severe cases (3 for placebo vs. 9 for test). If a scoring system of 0 = none; 1 = mild; 2 = moderate; 3 = moderately severe; 4 = severe; 5 = very severe is used, the placebo group would have a mean score of 2.00 and the test group, 2.08. Hence, insofar as mean scores are concerned, the bias appears slight.

If the bias is medically significant, it would appear to be in the favor of the placebo group. That is, if there is in fact no difference between the test and control group treatments, the results might be expected to show the placebo more effective because the severity of the cold symptoms were initially greater in the test group.

Objective Observations

In Tables 2 and 3 (pages 8 and 9), columns (1) show that the mean nasal airway resistance at 0 minutes for the placebo group was 4.99 cm H_2O/1 min. @ 1/sec. flow (25 observations) and 5.29 for the test group (25 observations).

These results agree with the subjective results in that the initial severity of nasal congestion in the placebo group was less than that of the active group. By the application of the standard "t" test it was found that the difference between the 2 groups was not statistically significant at the 5% level ($t = 0.30/0.1821 = 1.65$; the critical "t" value for 48 df at the 5% level is 2.01).

(continuted on page 10)

Table 2. Placebo Tablets. Calculation of per cent change in nasal airway resistance (cm H_2O/l/ min @ 0.5 l/sec flow) at the times indicated following administration of the tablets with reference to the patient's base line nasal airway resistance measured at 0 minutes.

(Source of Data: Table 1 in Vol 1 Compilation of Raw Data BEI 1025a)

Note: Cf paragraph Calculation for further explanation

Subject No.	Nasal Airway Resistance at 0 min.	Difference in nasal airway resistance between 0 min value and value at indicated times				
		15 min	30 min	60 min	120 min	Sum
	(1)	(2)	(3)	(4)	(5)	(6)
4	5.66	2.34	-1.26	-2.76	-0.26	3.72
12	5.85	-0.40	0.00	-0.90	0.05	4.60
20	4.60	1.35	1.05	0.75	0.20	7.95
27	4.30	0.15	1.55	-0.55	-0.25	5.20
37	5.17	-0.02	-0.47	-2.47	0.33	2.57
41	4.91	0.54	-1.50	1.44	-1.11	4.08
49	6.13	0.37	0.67	-0.73	-0.98	5.46
58	5.58	0.42	-0.27	-0.13	0.42	6.01
68	5.11	0.79	0.94	0.69	0.49	8.02
77	5.23	-0.28	0.02	0.87	-0.83	5.01
82	5.78	-3.93	-0.38	0.32	0.22	2.01
96	4.66	0.24	0.44	0.19	0.79	6.32
97	4.85	0.75	0.15	0.45	-0.45	5.75
110	4.93	0.02	-0.37	-1.08	-1.08	2.41
115	4.31	0.14	-1.06	-0.96	-0.16	2.27
126	5.55	-0.15	-0.60	-0.05	0.00	4.75
134	4.96	-1.51	-1.21	-1.76	-0.16	0.32
138	3.70	-0.15	-0.20	-0.95	1.55	3.95
149	5.40	0.50	-2.20	-2.30	-1.10	0.30
155	4.91	-0.66	0.29	0.39	-0.21	4.72
167	5.06	0.49	-2.41	-2.51	-1.01	-0.38
175	4.56	-0.21	-0.91	-0.56	-0.31	2.57
182	4.10	0.20	-0.05	-0.20	-0.10	3.95
187	4.25	0.05	0.05	-0.30	-0.55	3.50
195	5.25	-0.65	-0.15	-2.70	-2.35	-0.60
Sum 1	124.81	0.19	-7.9	-15.81	-6.86	94.43
Sum 2	124.81	125.00	116.91	109.00	131.67	
Average of sum values	4.99	5.00	4.68	4.36	5.27	
% Change from base line		+0.15	-6.33	-12.67	+5.50	

BEI 1025a

Table 3. Phenylephrine HCl (5 mg) Tablets. Calculation of per cent change in nasal airway resistance (cm H_2O/l/ min @ 0.5 l/sec flow) at the times indicated following administration of the tablets with reference to the patient's base line nasal airway resistance measured at 0 minutes.
(Source of data: Table 1 in Vol 2 Compilation of Raw Data BEI 1025a)
Note: Cf paragraph Calculation for further explanation

Subject No.	Nasal Airway Resistance at 0 min. (1)	Difference in nasal airway resistance between 0 min value and value at indicated times: 15 min (2)	30 min (3)	60 min (4)	120 min (5)	Sum (6)
5	7.10	-0.90	-0.85	-3.10	-2.55	-0.30
9	6.30	-0.90	-3.55	-3.65	-2.35	-4.15
21	5.78	0.12	-1.73	-1.88	-0.53	1.76
25	6.05	0.30	-0.25	-2.20	-3.45	0.45
34	5.36	0.44	-1.46	-0.56	-1.26	2.52
43	6.05	-0.35	-3.05	-2.30	-1.70	-1.55
50	5.56	-0.96	-0.91	-2.81	-1.61	-0.73
64	6.01	-0.06	-1.51	-1.61	-1.41	1.42
67	5.80	-1.15	-0.35	-0.50	-1.40	2.40
76	5.10	0.05	-1.65	-1.10	-1.50	0.90
83	5.25	-1.15	-0.80	-0.80	-2.50	0.00
94	4.88	-0.73	0.01	-0.93	-3.23	0.06
100	5.25	-1.00	-0.55	-2.90	-1.45	-0.65
106	4.25	0.00	0.20	-0.95	-1.25	2.95
113	5.36	-0.36	-1.91	-1.66	0.44	1.87
122	5.35	0.45	-1.30	-1.40	0.20	3.30
130	4.16	-0.16	-1.36	-1.46	-0.71	0.47
139	5.06	-2.26	-2.31	-2.26	-2.51	-4.28
147	4.16	-1.66	-0.61	-1.21	-0.66	0.02
153	4.90	-1.20	0.10	-1.20	-1.20	0.90
165	5.20	-0.85	0.15	-0.45	-0.95	3.10
170	4.91	-1.36	-1.61	-0.86	-2.61	-1.53
179	4.78	-0.68	-1.88	-0.48	0.27	2.01
189	4.71	-0.41	0.24	-0.06	0.24	4.72
194	4.31	-0.26	-0.41	-1.06	-0.46	2.12
Sum 1	132.34	-15.04	-27.29	-37.39	-34.64	17.98
Sum 2	132.34	117.30	105.05	94.95	97.70	
Mean of sum values	5.29	4.69	4.20	3.80	3.90	
% Change from base line		-11.37	-20.62	-28.25	-26.18	

Results and Discussion, contd.

Comparableness of the test and control groups, contd.

Objective-Subjective Study BEI 1025a, contd.

Severity of initial nasal congestion, contd.

Objective Observations, contd.

Conclusion: There was comparableness of the pertinent variables age, weight, height, race, sex, initial presenting symptoms, severity of initial presenting symptoms, and initial airway resistance in the test and controls groups in the BEI 1025a study.

Subjective Study BEI 1025a

Inspection of Table 6 (page 11) shows that in the test and control groups (Men + Women), there was comparableness of the pertinent variables ages, weight, height, race, sex, and symptoms, but there appears to be a difference in the severity of the initial presenting symptoms. Using the scoring system cited in Objective-Subjective Study BEI 1025a, Subjective Observations, the initial mean scores of nasal congestion was found to be: test group, 1.82; placebo group, 1.57.

When the statistical significance of this difference is tested using the method of Dunn, O. J. (Multiple Comparisons Using Rank Sums. Technometrics 6(3):241-252. August 1964), it was found to be statistically significant at the 5% level. (The critical value for the 5% level is 1.96, the calculated value for the difference is 1.97.)

The distribution of men and women within the test and control groups is different: control group, 48% men, 50% women; test group, 35% men, 65% women. However, this difference is not statistically significant at the 5% level. (Calculated Chi^2 is 2.22 vs. the critical value of 3.84).

Conclusion: Although the test and control groups were comparable as to age, weight, height, race, sex, and initial presenting cold symptoms, the initial severity of nasal congestion symptoms was greater in the test group (mean score = 1.82) than in the placebo group (mean score = 1.57).

If the results are biased because of this initial imbalance, the bias would appear to be in favor of the placebo. That is, if in fact there was no difference between the test and control treatments, the results might be expected to show that the placebo treatment was more effective because the severity of the nasal congestion symptoms were initially greater in the test group.

(continued on page 12)

Table 6. Patient population parameters in the test and control groups for Subjective Study BEI 1025b. (Source of data: Table 3 in Compilation of Raw Data for Subjective Data, Volumes 3 & 4)

			Age (yrs)	Wt (lbs)	Ht ft	Ht in	Race* White	Negro	Oriental	Indian	Filipino	Sex* Male	Female	Initial presenting symptoms & severity: symptoms StufNo*	RunNo*	Sneez*	ItchNo*	Cough*	MusAch*	HdAche*	Oral T °F	severity of nasal congestion* Mild	Mod	ModSevr	Sevr	VSevr
			(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)	(21)	(22)	(23)	(24)
Men	Placebo	Mean	53.7	185	5	11	32	0	0	0	0	32	0	36	33	33	1	33	33	20	99.4	14	21	1	0	0
		Range	16 – 77	118 – 283	5 – 6	4 – 3															98.8 – 100.3					
	Active	Mean	45.3	186	5	10	29	0	0	0	0	26	0	22	26	24	1	26	26	14	99.5	6	15	4	1	0
		Range	16 – 82	102 – 273	5 – 6	0 – 1															99 – 100					
Women	Placebo	Mean	56.1	138	5	4	37	2	0	0	0	0	37	37	39	37	2	33	34	19	99.5	24	10	5	0	0
		Range	18 – 78	99 – 212	5 – 5	0 – 7															98.6 – 102.6					
	Active	Mean	52.2	142	5	4	38	1	0	0	0	0	37	37	37	37	2	37	35	31	99.4	19	25	4	1	0
		Range	16 – 83	102 – 214	5 – 5	0 – 8															98.0 – 100.2					
Men + Women	Placebo	Mean	53.0	161	5	7	73	2	0	0	0	36	37	75	73	72	3	71	67	39	99.9	38	31	6	0	0
		Range	16 – 78	99 – 283	5 – 6	4 – 3															98.8 – 100					
	Active	Mean	53.0	157	5	6	74	1	0	0	0	26	39	75	75	75	3	73	77	45	99.4	25	30	8	2	0
		Range	16 – 83	102 – 273	5 – 6	0 – 1															99 – 100					

*The numbers in the table are the number of patients.

Results and Discussion, contd.

Comparableness of the test and control groups, contd.

Objective-Subjective Study BEI 1025a + Subjective Study BEI 1025b.

The subjective data obtained in the BEI 1025a + BEI 1025b studies are pooled and presented in Table 7 (page 13).

Firstly, the comparableness of the test groups are examined from 2 aspects, namely: initial presenting symptoms as judged by the patients themselves for each symptom (based on Table 2 in Volumes 1 through 4 Compilation of Raw Data for BEI 1025a and BEI 1025b) and as judged by the investigator for the overall severity of the initial presenting symptom of nasal congestion (based on Table 3 in Volumes 1 through 4 Compilation of Raw Data for BEI 1025a and BEI 1025b). Secondly, the comparableness of the test groups are examined further by the other evidence shown in Table 7.

Firstly:

Patients' evaluation of their initial pretreatment severity and kind of cold symptoms: Fig. 5, page 14, shows that the test and control groups were comparable on the basis of the patients' evaluation of their initial pretreatment severity and kind of cold symptoms.

Investigator's evaluation of the patients' initial severity of nasal congestion: The data for this evaluation is found in Table 3 as cited above. Using the scoring system cited in Objective-Subjective Study BEI 1025a, Subjective Observations, page 7, the initial mean scores of nasal congestion were: test group, 1.89; placebo group, 1.68. When the statistical significance of the difference is tested by the method of Dunn (loc cit), it was found not statistically significant at the 5% level. The critical value for the 5% level is 1.96; the calculated value for the observed difference is 1.83.)

Secondly:

Inspection of Table 7 shows that in the test and control groups (Men + Women), there was comparableness of the pertinent variables age, weight, height, race, and symptoms but there appears to be a difference in severity of the patients' initial severity of nasal congestion, as discussed above, and possibly there is a disproportionality in the distribution of the sexes within groups between the groups. That is, the distribution of men

(continued on page 15)

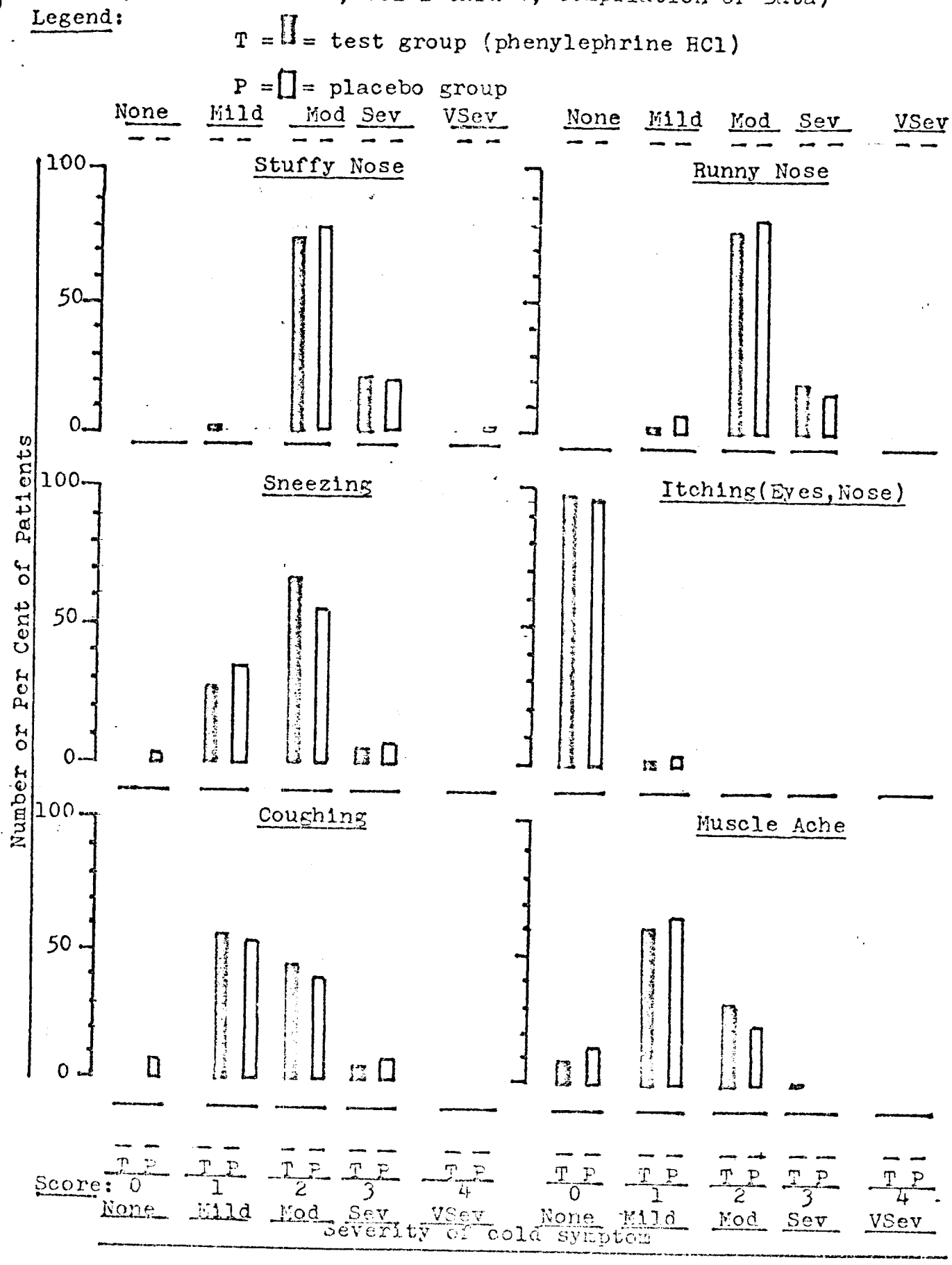
Table 7. Patient population parameters in the test & control groups for the Objective-subjective Study 1025a + Subjective Study 1025b (Source: Table 3, Vol 1 thru 4, Compilation of Data)

			Age (yrs)	Wt (lbs)	Ht ft	Ht in	Race* White	Negro	Oriental	Indian	Fillipino	Sex* Male	Female	Initial presenting symptoms & severity: symptoms StufNo*	RunNo*	Sneez*	ItchNo*	Cough*	MusAch*	HdAche*	Oral'l at	severity of nasal congestion* Mild	Mod	ModSevr	Sevr	VSevr
Men	Placebo	Mean	50.2	181.5	5	10	99	0	0	0	0	99	0	47	47	42	2	45	47	50	99.9 97.7	14	23	4	1	0
		Range	13 – 71	118 – 283	5 – 6	1 – 3															98.3 – 100					
	Active	Mean	47.3	180.9	5	8	99	0	0	0	0	35	0	35	35	35	1	35	32	19	97.5	8	18	8	1	0
		Range	16 – 82	102 – 273	5 – 6	0 – 1															99 – 100					
Women	Placebo	Mean	55.2	142.1	5	4	97	2	0	0	0	0	57	57	57	57	2	57	53	53	97.5	29	17	5	0	0
		Range	18 – 78	90 – 268	5 – 5	0 – 7															99 – 100					
	Active	Mean	52.7	144.7	5	4	93	2	0	0	0	0	57	57	55	55	2	55	50	37	97.4	29	21	9	1	0
		Range	16 – 83	99 – 216	5 – 6	0 – 0															99 – 100					
Men + Women	Placebo	Mean	52.8	161	5	7	98	2	0	0	0	99	57	104	104	97	4	99	83	53	98.4	43	17	9	1	0
		Range	13 – 78	99 – 283	5 – 6	0 – 3															98.3 – 100					
	Active	Mean	50.8	157	5	5	99	2	0	0	0	35	35	42	42	42	3	40	33	58	97.4	32	17	7	2	0
		Range	16 – 83	99 – 273	5 – 6	0 – 1															99 – 100					

*The numbers in the table are the number of patients.

Fig 5. Comparableness of initial pretreatment severity of cold symptoms (as judged by the patients themselves) in the test (100 patients) and placebo (100 patients) groups.

(Source: Table 2, Vol 1 thru 4, Compilation of Data)



Results and Discussion, contd.

Comparableness of test and control groups, contd.

Objective-Subjective Study BEI 1025a + Subjective Study BEI 1025b, contd.

Secondly, contd.

and women within the test and control groups was: test, 35% men, 65% women; placebo, 49% men, 51% women. The difference is not statistically significant at the 5% level. (calculated Chi^2 value is 3.46, the critical value is 3.84.)

Conclusion: The test and control groups were comparable as to age, weight, height, race, initial presenting cold symptoms. Although the differences between the groups as to initial severity of nasal congestion and sex distribution are not statistically significant at the 5% level, this does not preclude that a bias did or could arise from this source. If there is an inbalance because of inbalance in initial severity of nasal congestion, the effect is in favor of the placebo group because the initial sympoms of nasal congestion were more severe in the test group. If there is bias introduced because of sex inbalance, the direction of the bias is unknown because the nature of the sex effect, if any, on response is unknown.

Difference in response between the test & control groups

Objective-Subjective Study BEI 1025a

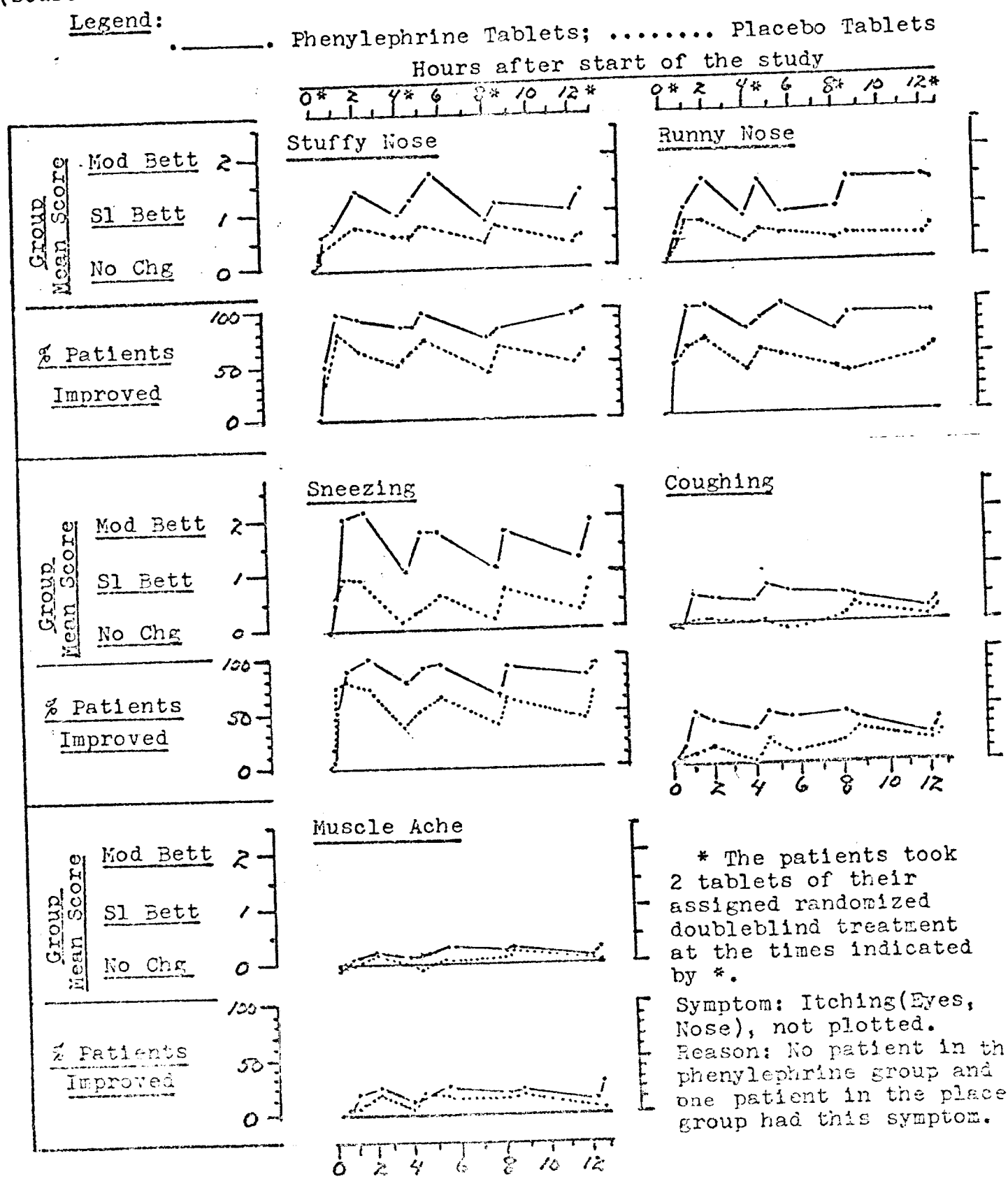
Subjective phase of the study. Fig. 1, page 16, provides a preliminary look at the response data. The data in Table 4 (located in the section marked with the index tab Appendix BEI 1025a placebo and active) were used to construct Fig. 1 as follows: All patients enumerated in Table 4 found in the rectangle bounded by the scores 0, 1, 2, 3, and 4 on the horizontal scale (these are the scores for the patient's initial severity of symptoms) and the scores 4, 3, 2, 1 on the vertical scale (these are the post treatment scores) are classed as "improved"; all patients found in the rectangle bounded by the scores 0, 1, 2, 3, 4 on the horizontal scale and 0 on the vertical scale, are classed as "no change"; and, all patients found in the rectangle bounded by the scores 0, 1, 2, 3, 4 on the horizontal scale and -1, -2, -3, -4 on the vertical scale, are classed as "worse".

Figure 1 therefore suggests that the phenylephrine treatment was more effective than the placebo in relieving the symptoms of stuffy nose, runny nose, and sneezing but probably not for coughing, and not for muscle ache. The sug-

(continued on page 17)

BEI 1025a

Fig 1. Subjective evaluation made by the 50 patients (25 active drug, 25 placebo) in study BEI 1025a(Objective Study) of their relief from the symptoms of stuffy nose, runny nose, sneezing, coughing, and muscle ache following the oral administration of phenylephrine HCl tablets (5 mg) or placebo tablets.
(Source of data: Appendix BEI 1025a placebo & active, Table 4)



* The patients took 2 tablets of their assigned randomized doubleblind treatment at the times indicated by *.

Symptom: Itching(Eyes, Nose), not plotted.
Reason: No patient in the phenylephrine group and one patient in the placebo group had this symptom.

Results and Discussion, contd.
Difference in response between the test & control groups, contd.
Objective-Subjective Study BEI 1025a, contd.
Subjective pase of the study, contd.

gestion derives from the fact that not only did a greater percentage of patients improve with phenylephrine treatment but the degree of improvement (mean score of the response) was also greater with phenylephrine than with the placebo.

This way of looking at the data is considered preliminary because it does not examine all the data available to better compare the test and control groups responses. A better method is presented in the section Objective-Subjective Study + Subjective Study (BEI 1025a + 1025b) which was uses all the data and subjects the data to statistical analysis.

Objective phase of the study. In tables 2 and 3, pages 8 and 9, the absolute and percent changes in nasal airway resistance is shown over the 2 hour post treatment time for the placebo and phenylephrine tablets. When presented in this way, not only can the correctness of the calculations be checked but also the agreement of 2 different statistical methods can be compared in assessing the significance of the difference between the test and control groups.

The correctness of the calculations of the percent change is evidenced by the fact that the sum of column 6 is equal to the sum in row sum 1 in Tables 8 and 9.

The "Sign Test" (Siegel, S. Nonparametric Statistics, pages 68-75, McGraw-Hill Book Co., Inc., 1956) and the "t" test (Snedecor, Statistical Methods, pages 62-68. Iowa State College Press, 1946) both agree that the phenylephrine treatment group had a greater reduction of nasal airway resistance than did the placebo group at a level of statistical significance greater than the 5% level. The magnitude of the numerical differences are given in Tables 2 and 3, pages 8 and 9, and presented graphically in Figures 2, page 18.

In Fig. 2, all the differences between the test and control groups are statistically significant at $P < 5\%$.

The following is an example of how Tables 2 and 3 can be used to obtain the statistical significance of the difference in response between the pre and post treatment of a given treatment: In Table 3, column 2, in 19 patients there was a reduction in nasal airway resistance 15 minutes after

(continued on page 19)

Fig 2 . Comparison of the mean absolute and per cent change of nasal airway resistance, determined by electronic posterior rhinometry, over a 2 hour period following the oral administration of two tablets as a single dose of either phenylephrine HCl tablets (5 mg) or placebo tablets in two groups of 25 patients having upper respiratory congestion associated with common cold in a double blind study.

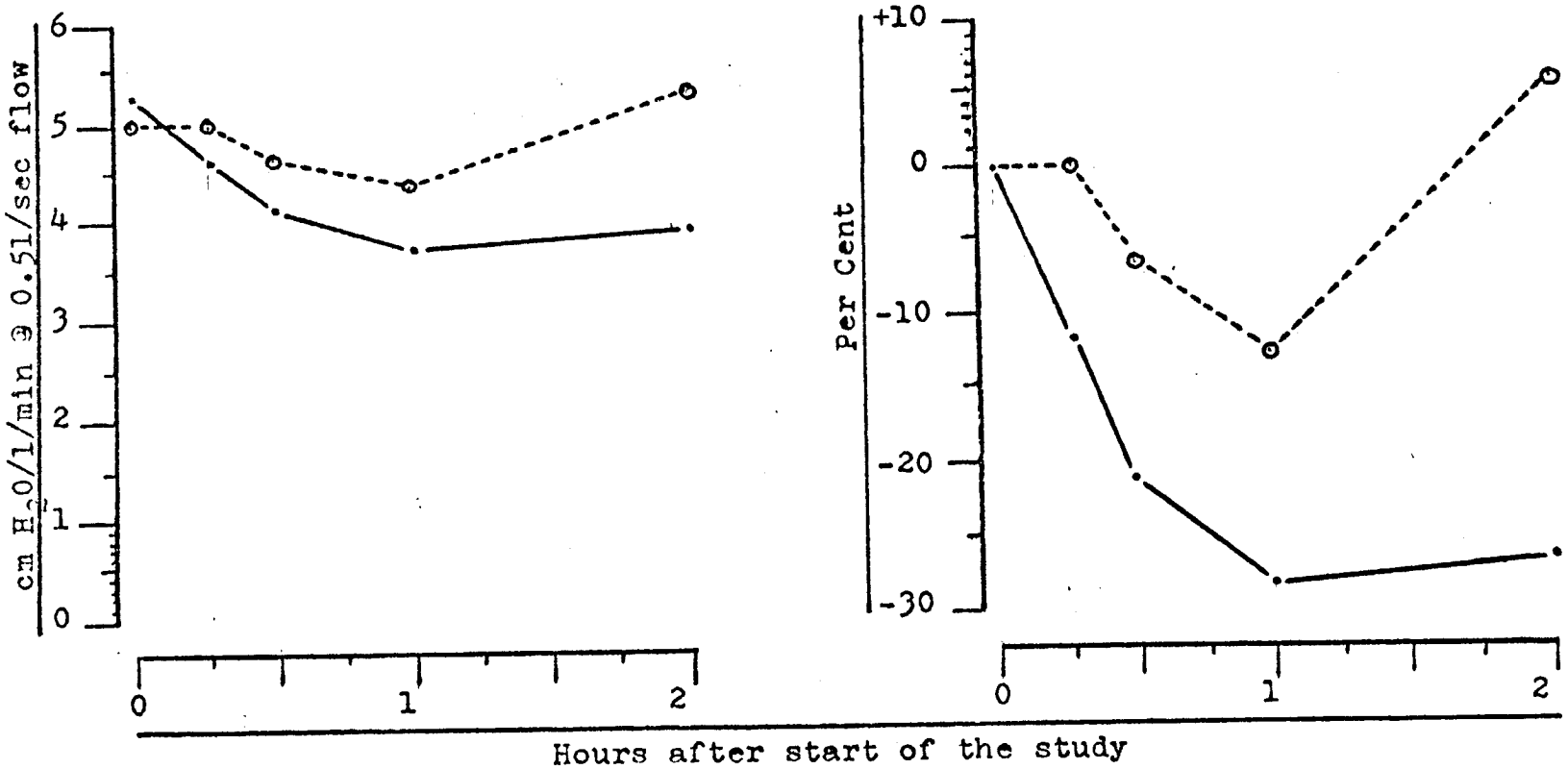
(Source: Table 1, Vol land 2, Compilation of Raw Data)

Absolute Change

Per Cent Change

Resistance:+(increased); -(decreased)

Legend: .———. Phenylephrine HCl; o--------o Placebo



All of the post treatment differences in nasal airway resistance responses between phenylephrine HCl vs. placebo at corresponding hours in this 50 patient study are statistically significant at P ≦ 5%.

Page 18

Results and Discussion, contd.

Difference in response between the test & control groups, contd.

Objective-Subjective Study BEI 1025a, contd.

Objective phase of the study contd.

phenylephrine treatment and in 6 patients an increase. According to the "Sign Test", the odds for this to happen in the absence of a genuine difference is P = .007 (one-tailed).

Application of the "t" test shows that all of the differences between the test and control groups at corresponding times are significant at P < 5%. Thus, the critical value of "t" is 2.01 for P = 0.05 at 48 df. In each case, the calculated value for "t" exceeded the critical value, i.e., for 15 minutes, t = 2.37; 30, 2.81; 60, 2.87, and 120, 4.17.

Subjective Study BEI 1025b

A preliminary overall view of the subjective response for the 150 patients is shown in Fig. 3, page 20.

The data in Table 5 (located in the section marked with the index tab Appendix BEI 1025b placebo and active) were used to construct Fig. 3.

The method for obtaining Fig. 3 is the same as described for Fig. 1, page 16, in the paragraph Subjective phase of the study, page 15. The comments and conclusions concerning the results in Fig. 1 are the same for Fig. 3. Fig. 3 suggests that phenylephrine was more effective than the placebo in relieving the symptoms of stuffy nose, runny nose, and sneezing but probably not for coughing and not for muscle ache.

A better method of evaluating these data is presented in Objective-Subjective Study BEI 1025a + Subjective Study BEI 1025b.

Objective-Subjective Study BEI 1025a + Subjective Study BEI 1025b.

The method of Dunn (loc cit) appears to be the optimal one to present the subjective findings and to evaluate their statistical significance. This is so because the Dunn method is designed not only to compare two or more samples and decide whether or not they come from identically distributed populations but also to decide which populations differ.

(continued on page 21)

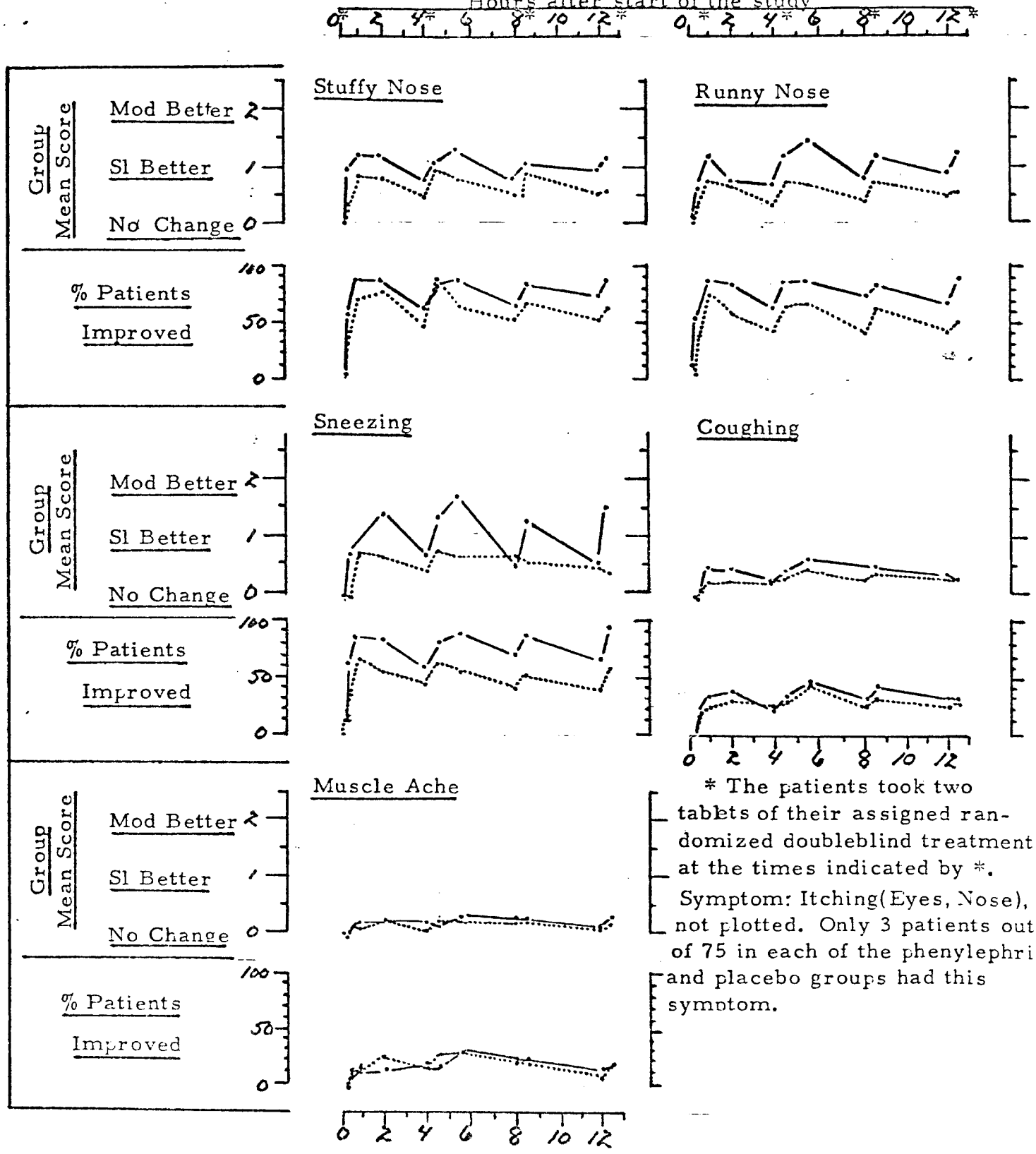
BEI 1025b

Fig 3. Subjective evaluation made by the 150 patients (75 active drug, 75 placebo) in study BEI 1025b(Subjective Study) of their relief from the symptoms of stuffy nose, runny nose, sneezing, coughing, and muscle ache following the oral administration of phenylephrine HCl tablets)5 mg) or placebo tablets.

(Source of data: Appendix BEI 1025b placebo and active Table 5)

Legend:

._____. Phenylephrine Tablets; ..... Placebo Tablets



* The patients took two tablets of their assigned randomized doubleblind treatment at the times indicated by *.

Symptom: Itching(Eyes, Nose), not plotted. Only 3 patients out of 75 in each of the phenylephri: and placebo groups had this symptom.

Results and Discussion, contd.

Difference in response between the test & control groups, contd.

Objective-Subjective Study BEI 1025a + Subjective Study BEI 1025b, contd.

Accordingly, using the 9 modality response rating scale ranging from +4 through -4 in increments as defined on Form 2 in the protocol, the data consisted of 2 sets of frequency distributions, one for the test and one for the control group for each of the 11 points in time after the administration of the assigned treatments. The 0 hour point was taken as 100 patients at 0 on the modality scale. The mean rank sums for each of the 23 distributions was calculated by the method of Dunn. A plot of the results is presented in Fig. 6, page 22.

Since there is a correlation between the score on the original 9 point modality scale and the mean rank sum scores, this relationship is also shown in Fig. 6 in order to express the results in terms of the original subjective scale.

The results for coughing and muscle ache were not included because Fig. 4, page 23 indicated no difference in response between the test and control groups for these symptoms.

The areas under the 0 to 12.5 hour curves have been calculated and included as a table in Fig. 6 to better portray the magnitude of the difference in effectivity of phenylephrine vs. placebo in the relief of cold symptoms, namely: 115% better than the placebo in relieving sneezing; 85% better in runny nose; and, 58% better in stuffy nose. The statistical significance of the difference between the test and control groups at corresponding points in time are also stated in Fig. 6.

Fig. 6 shows that phenylephrine was more effective than the placebo and that the placebo mimicked substantially the same cyclical up and down swings in the degree of relief but at a lesser response level coinciding with the times of remedication over the 12.5 hour period.

The findings from the objective measurements of nasal airway resistance (Fig. 2, page 18) are negatively correlated with the subjective observations of cold symptoms relief (Fig. 6, page 22). That is, the reduction of nasal airway resistance was correlated with increasing relief of the symptoms of sneezing, runny nose, and stuffy nose.

(continued on page 24)

BEI 1025a + 1025b

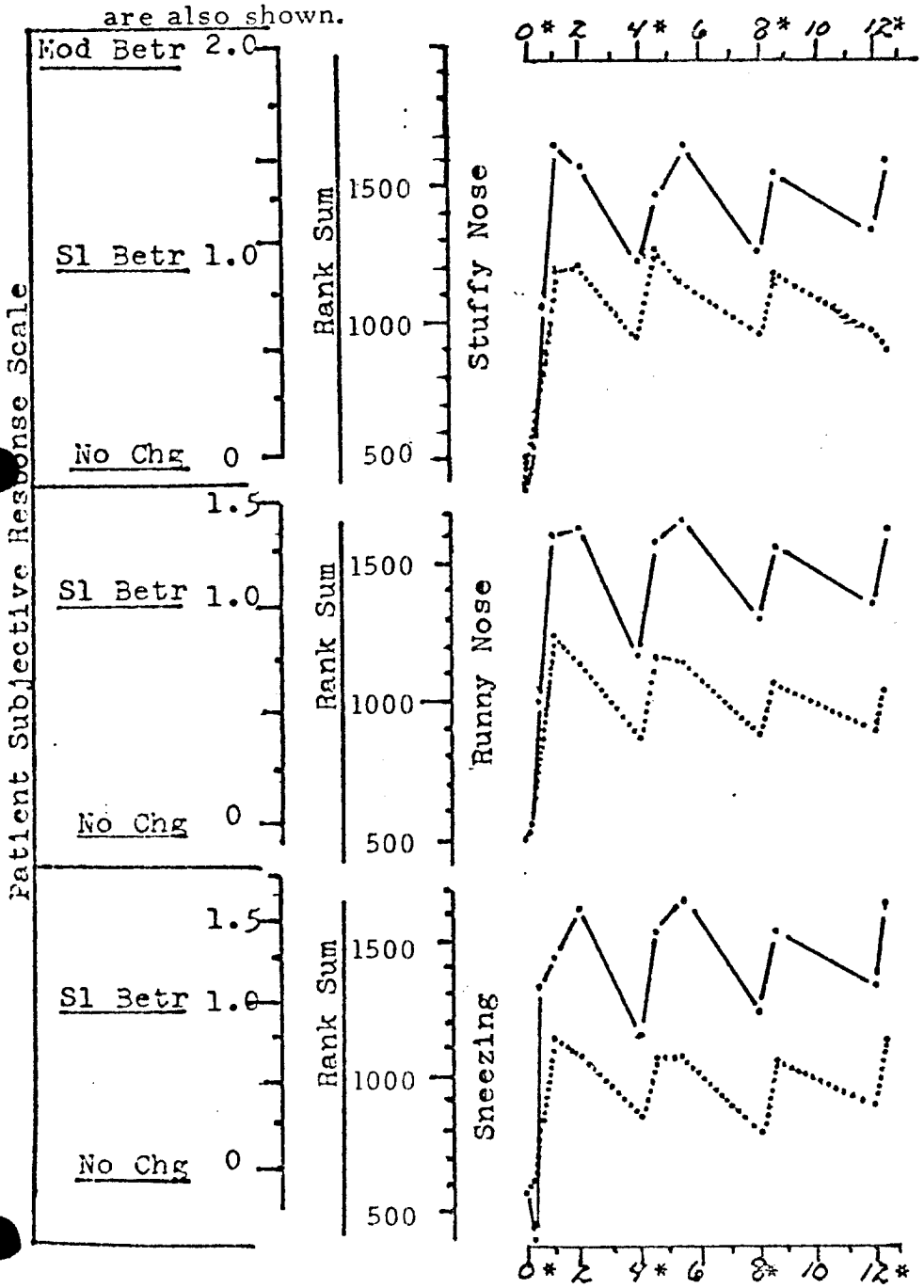
Fig 6. Mean rank sums of the scores made by 200 patients (100 active drug, 100 placebo) of their relief from the symptoms of stuffy nose, runny nose and sneezing following the oral administration of phenylephrine HCl tablets (5 mg) or placebo tablets.

(Source of data: Appendix BEI 1025 a + b, placebo & active, Table 9)

Legend:

._____. Phenylephrine Tablets ..... Placebo Tablets.

Note: The correlation between the mean rank sum scores and the scores made by the patients on the subjective response scale as well as the areas under the curves and per cent difference in area of the active drug relative to the placebo are also shown.



Area Under Curves
(rank sum/hr)

Symptom	Tablet		% Diff
	Active	Placebo	(1)-(2)/(2)
	(1)	(2)	(3)
Stuffy	11466	7270	57.7
Runny	11640	6291	85.0
Sneeze	10370	4832	114.6

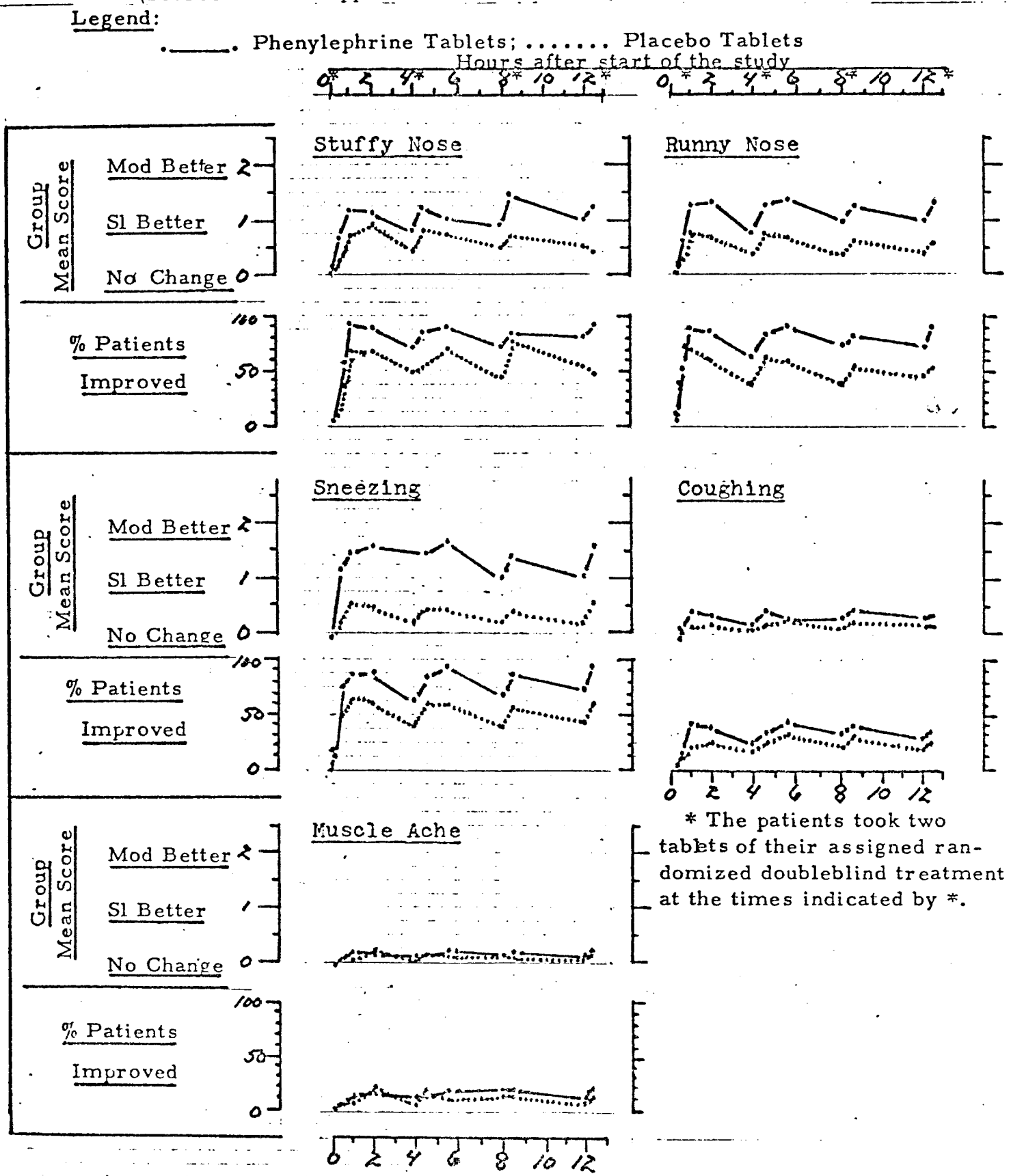
Differences in areas between active vs. placebo response for all 3 symtoms are statistically significant at P < 5%.

With the exception of the 0 and ½ hr values, the differences between active vs. placebo mean rank sums at corresponding times are statistically significant at P < 5%.

* The patients took two tablets of their assigned randomized doubleblind treatment at the times indicated by *.

Fig 4 . Subjective evaluation made by the 200 patients (100 active drug, 100 placebo) in BEI 1025a(Objective-Subjective Study with 50 patients) and BEI 1025b(Subjective Study with 150 patients) of their relief from the symptoms of stuffy nose, runny nose, sneezing, coughing, and muscle ache following the oral administration of phenylephrine HCl tablets (5 mg) or placebo tablets.

(Source of data: Appendix BEI 1024a + b, placebo & active, Table 9)



* The patients took two tablets of their assigned randomized doubleblind treatment at the times indicated by *.

Results and Discussion, contd.

Difference in response between the test & control groups, contd.

Objective-Subjective Study BEI 1025a + Subjective Study BEI 1025b, contd.

Patients' vs. Investigator's evaluation of the patients' overall degree of relief from cold symptoms following the prescribed course of treatment.

Fig. 7, page 25, shows that the patients' and the investigator's evaluation of the overall degree of the patients' subjective degree of relief from cold symptoms were in agreement as to the judgement that phenylephrine HCl tablets were more effective than the placebo tablets and as to the magnitude of the degree of relief obtained with phenylephrine tablets.

Effect of phenylephrine HCl tablets on blood pressure

Fig. 8, page 26 shows that the mean systolic blood pressure of the phenylephrine treated group was always higher (mean 1, 3 mm Hg higher; range 0.2 to 1.4) than that of the placebo group. The mean diastolic blood pressure of the phenylephrine group, with one exception, was always lower (mean 0.56 mm Hg lower; range -0.2 to 0.6) than that of the placebo group. These differences are not statistically significant at the 5% level.

Side Effects

The side effects observed in test and control groups are given in Table 8, page 27.

A summary of the findings are given in Summary, page 4.

Summary

A summary of all the findings is given in Summary, pages 2 through 4.

References

1. Cohen, B.M., Current Research Methodology in the Evaluation of Proprietary Medicine - II. Proceedings of a Conference Sponsored by the Scientific Development Committee of the Proprietary Association, Dec. 6, 1972. New York, New York.

2. Altschule, M.D., Editorial. The clinical insignificance of statistical significance, Med. Counterpoint, 3:6, 1971.

3. Gandevia, B., Hume, K.M., and Prime, F.F., Outpatient bronchodilator therapy, Lancet L:956, 1957.

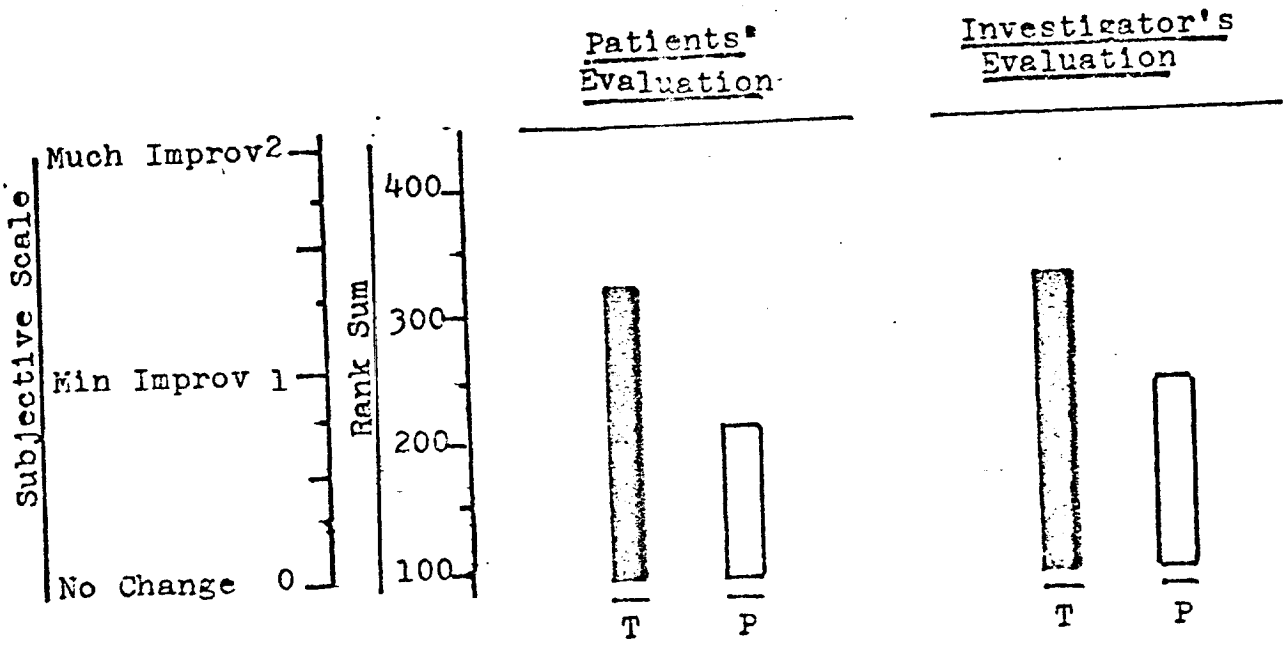
4. Freedman, B.J., Methods of comparing different bronchodilators in asthma, Bull. Physio-path. Resp., 8 :701, 1972.

BEI 1025a + 1025b

Fig 7. Comparison of Patients' vs. Investigator's evaluation of the magnitude of the patients' subjective degree of relief from cold symptoms following the course of the prescribed treatment.
(Source: Tables 3 & 4, Vol 1 thru 4, Compilation of Raw Data)

Legend: T = [▪] = test group (phenylephrine HCl), 100 patients

P = [ ] = placebo group, 100 patients



Conclusion: The following statements are consistent with the data at the 5% level of statistical significance:

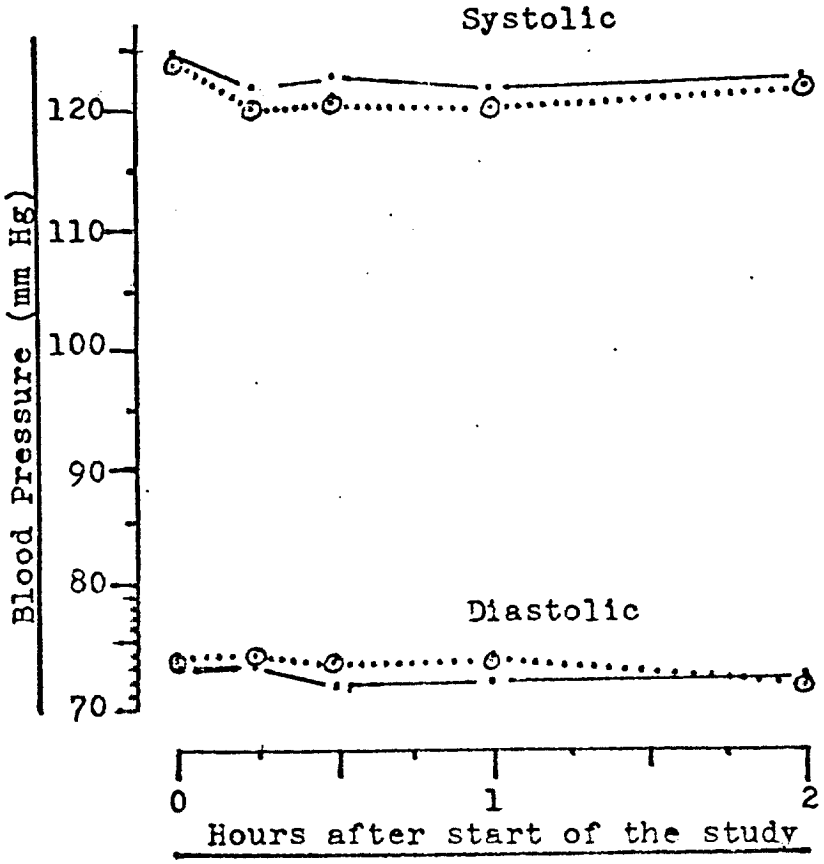
- The patients and the investigator both find that phenylephrine HCl 5 mg tablets were more effective than the placebo in relieving the symptoms of a cold.
- The patients and the investigator agree as to the degree of relief of cold symptoms obtained by the administration of the phenylephrine HCl 5 mg tablets.
- These subjective findings are not only in agreement with the objective findings that the phenylephrine tablet was more effective than the placebo tablets in relieving upper respiratory congestion but there is agreement with the observation made by Cohen[1] and other investigators[2,3,4] that patients are most likely to notice desirable medical or biological change in their own condition when the objective tests improve by a minimum of 20%.

Fig 8. Effect of phenylephrine HCl (5 mg) and placebo tablets on systolic and diastolic blood pressure (mm HG) following the oral administration of 2 tablets.

(Source: Table 1, Vol 1 & 2, Compilation of Raw Data)

Legend:*

.———. Phenylephrine HCl; ⊙.....⊙ Placebo



* Each point in the figure is the mean of 25 values.

Comment: The mean systolic blood pressure of the phenylephrine treated group was always higher (mean 1.3 mm Hg; range 0.2 to 1.4) than that of the placebo group.

The mean diastolic blood pressure of the phenylephrine group, with one exception, was always lower (mean 0.56 mm Hg; range -0.2 to 0.6) than that of the placebo group.

The differences are not statistically significant at the 5% level. In order to be statistically significant, the differences between two corresponding contrasting means would have to be about 3.8 mm Hg for systolic and 2.8 mm Hg for diastolic blood pressure.

Table 8. Side effects following the administration of the test and control treatments
(Source of data: Table 4 in Volumes 1 through 4 in Compilation of Raw Data (loc cit))

Legend:

Unbracketed numbers = number of patients
Bracketed number = the patient's code number
Active = phenylephrine HCl 5 mg tablets
Dose Regimen = 2 tablets ever 4 hours over a 12.5 hour period

Effect	Treatment Group	
	Active	Placebo
Dizzy	1 (30)	3 (96, 129, 155)
Dizzy + Flushing		1 (37)
Dry Mouth		3 (107, 176, 178)
Extrasystoles	1 (2)	
Felt Warm	3 (9,50,52)	1 (107, 176, 178)
Flush	1 (64)	
Headache		1 (107, 176, 178)
Nasal Dryness	1 (193)	
Nausea		2 (34, 159)
Slightly Shaky	1 (94)	
Total	8	11

BEI 1025 a

Table 4. Initial summation of data recorded on Form 3

Which symptom is recoded below (Circle one); (Stuffy Nose) Runny Nose, Sneezing, Itching (Eyes, Nose), Coughing, Muscle Ache

Data pertains to (Ck appropriate squares): ☒ Group 1; ☐ Group 2; ☒ Placebo; ☐ Active.

	0 hr					1/4 hr					1/2 hr					1 hr					2 hr					4 hr					
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	
4		1		1	4																										4
3		7		3	21																										3
2		17		2	34													1					3						1		2
1		0		1	1			1					6	1				9	10				9	3	1			9	3		1
0		0		0	0			15	7	1			10	5	1			3		1			4	4				7	3	1	0
-1		25			40			1					1	1				1					1					1			-1
-2																															-2
-3																															-3
-4																															-4
	Initial Mean Score = 1.0/25 = 2.4					% Better = 1/25 = 4% % No Chg. = 23/25 = 92% % Worse = 1/25 = 4% Mean score = (1−1)/25 = 0.0					% B = 7/25 = 28 % NC = 16/25 = 64 % W = 2/25 = 8 MS = (7−2)/25 = 0.2					% B = 20/25 = 80 % NC = 4/25 = 16 % W = 1/25 = 4 MS = (2+19−1)/25 = 0.8					% B = 16/25 = 64 % NC = 8/25 = 32 % W = 1/25 = 4 MS = (6+13−1)/25 = 0.72					% B = 13/25 = 52 % NC = 11/25 = 44 % W = 1/25 = 4 MS = (2+12−1)/25 = 0.52				

	4.5 hr					5.5 hr					8 hr					8.5 hr					12 hr					12.5 hr					
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	
4																															4
3																															3
2				1														1										1	1		2
1			9	4	1			14	5				7	4				11	4	1			10	3				9	5		1
0			5	2				2	2	1			10	3				5	3				5	4				7	1		0
-1			3					1							1								2		1					1	-1
-2																															-2
-3																															-3
-4																															-4
	% B = 15/25 = 60 % NC = 7/25 = 28 % W = 3/25 = 12 MS = (2+1−3)/25 = 0.0					% B = 19/25 = 76 % NC = 5/25 = 20 % W = 1/25 = 4 MS = (19−1)/25 = 0.72					% B = 11/25 = 44 % NC = 13/25 = 52 % W = 1/25 = 4 MS = (11−1)/25 = 0.40					% B = 17/25 = 68 % NC = 8/25 = 32 % W = 0/25 = 0 MS = (2+16)/25 = 0.72					% B = 13/25 = 52 % NC = 9/25 = 36 % W = 3/25 = 12 MS = (13−3)/25 = 0.40					% B = 16/25 = 64 % NC = 8/25 = 32 % W = 1/25 = 4 MS = (2+14−1)/25 = 0.60				

BEI 1025 a

Table 4. Initial summation of data recorded on Form 3

Which symptom is recoded below (Circle one); Stuffy Nose, (Runny Nose), Sneezing, Itching (Eyes, Nose), Coughing, Muscle Ache

Data pertains to (Ck appropriate squares): ☒ Group 1; ☐ Group 2; ☒ Placebo; ☐ Active.

	0 hr					1/4 hr					1/2 hr					1 hr					2 hr					4 hr				
	0	10	2	Sco 8	9	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4		0		4	0																									
3		7		3	21																									
2		18		2	36								1					1	1					1					
1		0		1	0			2					8	3				10	5				12	5				6	4	
0		0		0	0			16	7				9	1				7	1				6	1				12	2	
-1	Sum	25			57								1	2															1	
-2																														
-3																														
-4																														

Initial Mean Score = 57/25 = 2.28

1/4 hr: % Better = 2/25 = 8; % No Chg. = 23/25 = 92; % Worse = 0/25 = 0; Mean Score = (2)/25 = 0.08

1/2 hr: % B = 12/25 = 48; % NC = 10/25 = 40; % W = 3/25 = 12; MS = (2+11-3)/25 = 0.40

1 hr: % B = 17/25 = 68; % NC = 8/25 = 32; % W = 0/25 = 0; MS = (4+15)/25 = 0.76

2 hr: % B = 18/25 = 72; % NC = 7/25 = 28; % W = 0/25 = 0; MS = (2+17)/25 = 0.76

4 hr: % B = 10/25 = 40; % NC = 14/25 = 56; % W = 1/25 = 4; MS = (10-1)/25 = 0.36

	4.5 hr					5.5 hr					8 hr					8.5 hr					12 hr					12.5 hr				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4																														
3																														
2				2				1										2										1	1	
1			11	2				5	4				7	4				6	2				10	4				9	4	
0			5	2				8	3				10	2				10	5				6	2				8	1	
-1			2	1				1					1	1										2	1				1	
-2																														
-3																														
-4																														

4.5 hr: % B = 15/25 = 60; % NC = 7/25 = 28; % W = 3/25 = 12; MS = (4+13-3)/25 = 0.54

5.5 hr: % B = 13/25 = 52; % NC = 11/25 = 44; % W = 1/25 = 4; MS = (2+12-1)/25 = 0.52

8 hr: % B = 11/25 = 44; % NC = 12/25 = 48; % W = 2/25 = 8; MS = (1+1)/25 = 0.10

8.5 hr: % B = 10/25 = 40; % NC = 15/25 = 60; % W = 0/25 = 0; MS = (4+5)/25 = 0.36

12 hr: % B = 14/25 = 56; % NC = 8/25 = 32; % W = 3/25 = 12; MS = (14-3)/25 = 0.44

12.5 hr: % B = 15/25 = 60; % NC = 9/25 = 36; % W = 1/25 = 4; MS = (4+13-1)/25 = 0.64

BEI 1025 a

Table 4. Initial summation of data recorded on Form 3

Which symptom is recoded below (Circle one); Stuffy Nose, Runny Nose, (Sneezing) Itching (Eyes, Nose), Coughing, Muscle Ache

Data pertains to (Ck appropriate squares): ☒ Group 1; ☐ Group 2; ☒ Placebo; ☐ Active.

	0 hr					1/4 hr					1/2 hr					1 hr					2 hr					4 hr					
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	
4		0		4	0																										4
3		3		3	9												1					1	1								3
2		15		5	30								2				2	1	1			1	2						1		2
1		7		7	7		1	3				3	11	2			3	10	1			3	8	2			3	3			1
0		0		0	0		3	6	1					1			1	3	1			2	3				3	9			0
-1	Sum	25			46		3	6	3			3	2	1				2					1	1			1	3	2		-1
-2																															-2
-3																															-3
-4																															-4

Initial Mean Score = 46/25 = 1.84

% Better = 4/25 = 16
% No Chg. = 10/25 = 40
% Worse = 11/25 = 44
Mean Score = (4−11)/25 = −0.28

% B = 18/25 = 72
% NC = 1/25 = 4
% W = 6/25 = 24
MS = (4+16−6)/25 = 0.56

% B = 19/25 = 76
% NC = 4/25 = 16
% W = 2/25 = 8
MS = (5+3+14−2)/25 = 0.92

% B = 18/25 = 72
% NC = 5/25 = 20
% W = 2/25 = 8
MS = (3+6+13−2)/25 = 0.92

% B = 7/25 = 28
% NC = 12/25 =
% W = 6/25 = 24
MS = (2+6−6)/25 = 0.08

	4.5 hr					5.5 hr					8 hr					8.5 hr					12 hr					12.5 hr					
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	
4																															4
3								1										1					1					1			3
2		1	1				1	1									1						1				2	1			2
1		5	5	1			3	9	1			5	5				3	11				3	6				2	9	2		1
0		1	4	2				3	1			2	6	1			3	3	2			2	4	2			3	3	1		0
-1			5				3	1	1				1	3					1			2	3	1				1			-1
-2																															-2
-3																															-3
-4																															-4

% B = 13/25 = 52
% NC = 7/25 = 28
% W = 5/25 = 20
MS = (2+11−5)/25 = 0.32

% B = 16/25 = 64
% NC = 4/25 = 16
% W = 5/25 = 20
MS = (3+4+13−5)/25 = 0.60

% B = 10/25 = 40
% NC = 9/25 = 36
% W = 6/25 = 24
MS = (10−6)/25 = 0.16

% B = 16/25 = 64
% NC = 8/25 = 32
% W = 1/25 = 4
MS = (3+2+14−1)/25 = 0.76

% B = 11/25 = 44
% NC = 8/25 = 32
% W = 6/25 = 24
MS = (3+2+9−4)/25 = 0.32

% B = 17/25 = 68
% NC = 7/25 = 28
% W = 1/25 = 4
MS = (3+6+13−1)/25 = 0.84

BEI 1025 Ca

Table 4. Initial summation of data recorded on Form 3

Which symptom is recoded below (Circle one); Stuffy Nose, Runny Nose, Sneezing, Itching (Eyes, Nose), Coughing, Muscle Ache

Data pertains to (Ck appropriate squares): ☒ Group 1; ☐ Group 2; ☒ Placebo; ☐ Active.

	0 hr					1/4 hr					1/2 hr					1 hr					2 hr					4 hr				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4		0		0	0																									4
3		0		1	0																									3
2		0		2	0																									2
1		1		3	3																						1			1
0		24			96	24	1				24	1				24	1				24	1				24				0
-1		25			74																									1
-2																														2
-3																														3
																														4

Initial Mean Score =

% Better = 0/25 = 0
% No Chg = 25/25 = 100
% Worse = 0/25 = 0
Mean Score =

% B = 0/25 = 0
% NC = 25/25 = 100
% W = 0/25 = 0
MS =

% B = 0/25 = 0
% NC = 25/25 = 100
% W = 0/25 = 0
MS =

% B = 0/25 = 0
% NC = 25/25 = 100
% W = 0/25 = 0
MS =

% B = 1/25 = 4
% NC = 24/25 = 96
% W = 0/25 = 0
MS =

	4.5 hr					5.5 hr					8 hr					8.5 hr					12 hr					12.5 hr				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4																														4
3																														3
2																														2
1																														1
0	24	1				24	1				24	1				24	1				24	1				24	1				0
-1																														-1
-2																														-2
-3																														-3

% B = 0/25 = 0
% NC = 25/25 = 100
% W = 0/25 = 0
MS =

% B = 0/25 = 0
% NC = 25/25 = 100
% W = 0/25 = 0
MS =

% B = 0/25 = 0
% NC = 25/25 = 100
% W = 0/25 = 0
MS =

% B = 0/25 = 0
% NC = 25/25 = 100
% W = 0/25 = 0
MS =

% B = 0/25 = 0
% NC = 25/25 = 100
% W = 0/25 = 0
MS =

BEI 1025 a

Table 4. Initial summation of data recorded on Form 3

Which symptom is recoded below (Circle one); Stuffy Nose, Runny Nose, Sneezing, Itching (Eyes, Nose), (Coughing), Muscle Ache

Data pertains to (Ck appropriate squares): ☒ Group 1; ☐ Group 2; ☒ Placebo; ☐ Active.

	0 hr					1/4 hr					1/2 hr					1 hr					2 hr					4 hr				
	0	1/2	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4		0		4	0																									
3		0		3	0																									
2		11		2	22																									
1		12		1	12						1					1		1				1	2							
0		2		0	0	2	12	11			1	10	11			1	12	9			2	10	9			1	12	11		
-1		25			44							2						1				1				1				
-2																														
-3																														

Initial Mean Score = 44/25 = 1.76 (0.91)

% Better = 0/25 = 0; % No chg = 25/25 = 100; % Worse = 0/25 = 0; Mean Score = 0/25 = 0.0 (%B=0; MS=0.0)

% B = 1/25 = 4; % NC = 22/25 = 88; % W = 2/25 = 8; MS = (1-2)/25 = -0.04 (%B=0.0; MS=-0.04)

% B = 2/25 = 8; % NC = 22/25 = 88; % W = 1/25 = 4; MS = (2-1)/25 = 0.04 (%B=4.3; MS=-0.04)

% B = 3/25 = 12; % NC = 21/25 = 84; % W = 1/25 = 4; MS = (3-1)/25 = 0.08 (%B=13; MS=0.09)

% B = 0/25 = 0; % NC = 24/25 = 96; % W = 1/25 = 4; MS = -1/25 = -0.04 (%B=0.0; MS=0.0)

	4.5 hr					5.5 hr					8 hr					8.5 hr					12 hr					12.5 hr				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4																														
3																														
2																														
1		2	2				1	1				1	3				5	2				1	3				4	2		
0	2	10	7			1	10	9			2	9	9			2	7	9			2	10	8			2	8	9		
-1			2			1	1	1				1										1								
-2																														
-3																														

% B = 4/25 = 16; % NC = 17/25 = 72; % W = 2/25 = 8; MS = (4-2)/25 = 0.08 (%B=0.0; MS=0.00)

% B = 2/25 = 8; % NC = 20/26 = 80; % W = 3/25 = 12; MS = (2-3)/25 = -0.04 (%B=0.0; MS=0.0)

% B = 4/25 = 16; % NC = 20/25 = 80; % W = 1/25 = 4; MS = (4-1)/25 = 0.12 (%B=13; MS=0.13)

% B = 7/25 = 28; % NC = 18/25 = 72; % W = 0/25 = 0; MS = 7/25 = 0.28 (%B=28; MS=0.28)

% B = 4/25 = 16; % NC = 20/25 = 80; % W = 1/25 = 4; MS = (4-1)/25 = 0.12 (%B=13; MS=0.13)

% B = 6/25 = 24; % NC = 19/25 = 76; % W = 0/25 = 0; MS = (6)/25 = 0.24 (%B=24; MS=0.24)

BEI 1025 a

Table 4. Initial summation of data recorded on Form 3

Which symptom is recoded below (Circle one); Stuffy Nose, Runny Nose, Sneezing, Itching (Eyes, Nose), Coughing, Muscle Ache

Data pertains to (Ck appropriate squares): ☒ Group 1; ☐ Group 2; ☒ Placebo; ☐ Active.

	0 hr			Score		1/4 hr					1/2 hr					1 hr					2 hr					4 hr					
	0	1/2	2		4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	
4		0		4	0																										4
3		0		3	0																										3
2		6		2	12																										2
1		13		1	13								1			1						3	1					1			1
0		6		0	0	6	13	6			6	13	5				5	12	6		6	10	5			6	12	5			0
-1		25			25													1										1			-1
-2																															-2
-3																															-3
-4																															-4

Initial Mean score = 25/25 = 1.00 (1.32)

% Better = 0/25 = 0; % No Chg. = 25/25 · 100; % Worse = 0/25 = 0; Mean Score = 0/25 = 0.0 (%B = 0; MS = 0.0)

% B = 1/25 = 4; % NC = 24/25 = 96; % W = 0/25 = 0; MS = 1/25 (%B = 0.3; MS = 0.04)

% B = 1/25 = 4; % NC = 23/25 = 92; % W = 1/25 = 4; MS = (1-1)/25 (%B = 0; MS = 0.0)

% B = 4/25 = 16; % NC = 21/25 = 84; % W = 0/25 = 0; MS = (4)/25 (%B = 29; MS = 0.21)

% B = 1/25 = 4; % NC = 23/25 = 92; % W = 1/25 = 4; MS = (1-1)/25 (%B = 5.3; MS = 0.0)

	4.5 hr					5.5 hr					8 hr					8.5 hr					12 hr					12.5 hr					
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	
4																															4
3																															3
2																															2
1		11					2	1				3	1				2	3					2					1			1
0	6	4	6			6	10	4			6	10	5			6	11	3			6	13	4			6	13	5			0
-1							1	1																							-1
-2																															-2
-3																															-3
-4																															-4

% B = 4/25 = 16; % NC = 21/25 = 84; % W = 0/25 = 0; MS = 4/25 = 0.16 (%B = 21.1; MS = 0.21)

% B = 3/25 = 12; % NC = 20/25 = 80; % W = 2/25 = 8; MS = (3-2)/25 = 0.04 (%B = 15.9; MS = 0.05)

% B = 4/25 = 16; % NC = 21/25 = 84; % W = 0/25 = 0; MS = (4)/25 = 0.16 (%B = 21.1; MS = 0.21)

% B = 5/25 = 20; % NC = 20/25 = 80; % W = 0/25 = 0; MS = 6/25 = 0.24 (%B = 26.3; MS = 0.21)

% B = 2/25 = 8; % NC = 23/25 = 92; % W = 0/25 = 0; MS = 2/25 = 0.08 (%B = 10.5; MS = 0.21)

% B = 1/25 = 4; % NC = 24/25 = 96; % W = 0/25 = 0; MS = 1/25 = 0.04 (%B = 5.3; MS = 0.05)

BEI 1025 Ac

Table 4. Initial summation of data recorded on Form 3

Which symptom is recoded below (Circle one); (Stuffy Nose) Runny Nose, Sneezing, Itching (Eyes, Nose), Coughing, Muscle Ache

Data pertains to (Ck appropriate squares): ☐ Group 1; ☒ Group 2; ☐ Placebo; ☒ Active.

0 hr (Score)

	0	1	2	3	4
4		0		4	0
3		5		3	15
2		20		2	40
1		0		1	0
0		0		0	0
-1		25			55
-2					
-3					
-4					

Initial Mean Score = $\frac{55}{25}$ = 2.20

1/4 hr

	0	1	2	3	4
4					
3					
2					
1			1		
0			19	5	
-1					
-2					
-3					
-4					

% Better = 1/25 = 4.0
% No Chg. = 24/25 = 96.0
% Worse = 0/25 = 0.0

Mean Score = $\frac{1}{25}$ = 0.04

1/2 hr

	0	1	2	3	4
4					
3					
2			1		
1			8	14	
0			10	1	
-1			1		
-2					
-3					
-4					

% B = 13/25 = 52.0
% NC = 11/25 = 44.0
% W = 1/25 = 4.0

MS = $\frac{2+17-1}{25}$ = 0.52

1 hr

	0	1	2	3	4
4					
3			1		
2			7		
1			12	5	
0					
-1					
-2					
-3					
-4					

% B = 25/25 = 100
% NC = 0/25 = 0
% W = 0/25 = 0

MS = $\frac{3+14}{25}$ = 0.68

2 hr

	0	1	2	3	4
4					
3					
2			8	3	
1			11	2	
0			1		
-1					
-2					
-3					
-4					

% B = 24/25 = 96.0
% NC = 1/25 = 4.0
% W = 0/25 = 0.0

MS = $\frac{22+13}{25}$ = 1.4

4 hr

	0	1	2	3	4
4					
3					
2			2		
1			14	5	
0			4		
-1					
-2					
-3					
-4					

% B = 24/25 = 94.0
% NC = 4/25 = 16.0
% W = 0/25 = 0.0

MS = $\frac{4+19}{25}$ = 0.92

4.5 hr

	0	1	2	3	4
4					
3				1	
2			6	2	
1			10	2	
0			4		
-1					
-2					
-3					
-4					

% B = 24/25 = 94.0
% NC = 4/25 = 16.0
% W = 0/25 = 0.0

MS = $\frac{3+16+12}{25}$ = 1.24

5.5 hr

	0	1	2	3	4
4					
3					
2			9	3	
1			11	1	
0					
-1					
-2					
-3					
-4					

% B = 25/25 = 100
% NC = 0/25 = 0
% W = 0/25 = 0

MS = $\frac{4+24+12}{25}$ = 1.60

8 hr

	0	1	2	3	4
4					
3			3	2	
2			11	3	
1			6		
0					
-1					
-2					
-3					
-4					

% B = 19/25 = 76
% NC = 6/25 = 24
% W = 0/25 = 0

MS = $\frac{20+14}{25}$ = 0.96

8.5 hr

	0	1	2	3	4
4					
3			2		
2			5	3	
1			8	2	
0			5		
-1					
-2					
-3					
-4					

% B = 20/25 = 80
% NC = 5/25 = 20
% W = 0/25 = 0

MS = $\frac{6+16+10}{25}$ = 1.28

12 hr

	0	1	2	3	4
4					
3			3	1	
2			16	4	
1			1		
0					
-1					
-2					
-3					
-4					

% B = 24/25 = 96
% NC = 1/25 = 4
% W = 0/25 = 0

MS = $\frac{8+20}{25}$ = 1.12

12.5 hr

	0	1	2	3	4
4					
3			2		
2			3	14	
1			15	1	
0					
-1					
-2					
-3					
-4					

% B = 25/25 = 100
% NC = 0/25 = 0
% W = 0/25 = 0

MS = $\frac{6+14+15}{25}$ = 1.40

BEI 1025 a

Table 4. Initial summation of data recorded on Form 3

Which symptom is recoded below (Circle one); Stuffy Nose, (Runny Nose), Sneezing, Itching (Eyes, Nose), Coughing, Muscle Ache

Data pertains to (Ck appropriate squares): ☐ Group 1; ☒ Group 2; ☐ Placebo; ☒ Active.

	0 hr Score					1/4 hr					1/2 hr					1 hr					2 hr					4 hr					
	0	1/5	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	
4		0		4	0																									4
3		5		3	15																		1	1						3
2		20		2	40								1	1				10	3				12	3				1		2
1		0		1	0			1					7	3				10	2				7	1				15	2	1
0		0		0	0			19	5				10	1														4	2	0
-1		25			25								2																	-1
-2																														-2
-3																														-3
-4																														-4

Initial Mean Score = 55/25 = 2.2

% Better = 1/25 = 4
% No Chg = 24/25 = 96
% Worse = 0/25 = 0
Mean Score = 1/25 = .04

% B = 12/25 = 48
% NC = 11/25 = 44
% W = 2/25 = 8
MS = (4+10-2)/25 = 0.48

% B = 25/25 = 100
% NC = 0/25 = 0
% W = 0/25 = 0
MS = 26/25 = 1.04

% B = 25/25 = 100
% NC = 0/25 = 0
% NC = 0/25 = 0
MS = (6+30)/25 = 1.44

% B = 19/25 = 76
% NC = 6/25 = 24
% W = 0/25 = 0
MS = (2+18)/25 = 0.8

	4.5 hr					5.5 hr					8 hr					8.5 hr					12 hr					12.5 hr					
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	
4								1																						4
3			1	1														1	2				1	2						3
2			9	2				7	2				3	2				7	1				6	1				9	3	2
1			7	2				12	3				13	1				10	2				11	2				4	2	1
0			3										4	2				2					2					2		0
-1																														-1
-2																														-2
-3																														-3
-4																														-4

% B = 22/25 = 88
% NC = 3/25 = 12
% W = 0/25 = 0
MS = (6+22+9)/25 = 1.48

% B = 25/25 = 100
% NC = 0/25 = 0
% W = 0/25 = 0
MS = (4+19)/25 = 0.92

% B = 19/25 = 76
% NC = 6/25 = 24
% W = 0/25 = 0
MS = (10+14)/25 = 0.96

% B = 23/25 = 92
% NC = 2/25 = 8
% W = 0/25 = 0
MS = (9+16+12)/25 = 1.48

% B = 23/25 = 92
% NC = 2/25 = 8
% W = 0/25 = 0
MS = (9+14+13)/25 = 1.44

% B = 23/25 = 92
% NC = 2/25 = 8
% W = 0/25 = 0
MS = (24+11)/25 = 1.40

BEI 1025 a

Table 4. Initial summation of data recorded on Form 3

Which symptom is recoded below (Circle one); Stuffy Nose, Runny Nose, (Sneezing), Itching (Eyes, Nose), Coughing, Muscle Ache

Data pertains to (Ck appropriate squares): ☐ Group 1; ☒ Group 2; ☐ Placebo; ☒ Active.

	0 hr					1/4 hr					1/2 hr					1 hr					2 hr					4 hr					
	0	1/0	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	
4		0		4	0								1				1	1				1	1								4
3		1		3	3												2	3				2	5					1			3
2		15		2	30							1	3				4	6	1			4	6				1	5			2
1		9		1	9			2				3	5				1	4				2	3	1			7	6	1		1
0		6		0	0		8	11	1			2	2				1	1									1	2			0
-1		2			42		1	2				3	4	1														1		-1
-2																															-2
-3																															-3
-4																															-4
	Initial Mean Score = 42/25 = 1.68					% Better = 2/25 = 8 % No Chg = 20/25 = 80 % Worse = 3/25 = 12 Mean Score = (2 − 3)/25 = −0.04					% B = 13/25 = 52 % NC = 4/25 = 16 % W = 8/25 = 32 MS = (4+9+8−8)/25 = 0.48					% B = 23/25 = 92 % NC = 2/25 = 8 % W = 0/25 = 0 MS = (8+15+22+5)/20 = 2.0					% B = 25/25 = 100 % NC = 0/25 = 0 % W = 0/25 = 0 MS = (9+21+20+6)/25 = 2.2					% B = 21/25 = 84 % NC = 3/25 = 12 % W = 1/25 = 4 MS = (3+12+14−1)/25 = 1.12					

	4.5 hr					5.5 hr					8 hr					8.5 hr					12 hr					12.5 hr					
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	
4			1					3					1					3										3			4
3		2	1					1				1	4				3	3				2	3				2	3			3
2		14	6	1			3	4	1				1				1	2					5				4	3	1		2
1		1	5				5	7				5	5				4	6	1			3	7	1			2	6			1
0		1					1					2	4	1			1	1				1					1				0
-1		1										1										3									-1
-2																															-2
-3																															-3
-4																															-4
	% B = 33/25 = 92 % NC = 1/25 = 4 % W = 1/25 = 4 MS = (1+9+26+6−1)/25 = 1.20					% B = 24/25 = 96 % NC = 1/25 = 4 % W = 0/25 = 0 MS = (2+3+16+12)/25 = 1.72					% B = 17/25 = 68 % NC = 7/25 = 28 % W = 1/25 = 4 MS = (4+15+2+10−1)/25 = 1.20					% B = 23/25 = 92 % NC = 2/25 = 8 % W = 0/25 = 0 MS = (12+18+6+11)/25 = 1.89					% B = 21/25 = 84 % NC = 1/25 = 4 % W = 3/25 = 12 MS = (15+10+11−3)/25 = 1.32					% B = 24/25 = 96 % NC = 1/25 = 4 % W = 0/25 = 0 MS = (12+15+16+8)/25 = 2.04					

BEI 1025 a

Table 4. Initial summation of data recorded on Form 3

Which symptom is recoded below (Circle one); Stuffy Nose, Runny Nose, Sneezing, (Itching (Eyes, Nose)), Coughing, Muscle Ache

Data pertains to (Ck appropriate squares): ☐ Group 1; ☒ Group 2; ☐ Placebo; ☒ Active.

	0 hr					1/4 hr					1/2 hr					1 hr					2 hr					4 hr					
	0	No	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	
4		0		4	0																									4
3		0		3	0																									3
2		0		2	0																									2
1		0		1	0																					1				1
0		25		0	0	25					25					25					25					24					0
-1					0																									-1
-2																														-2
-3																														-3
-4																														-4
	Initial Mean Score = 0.0					% Better = 0/25 = 0 % No Chg = 25/25 = 100 % Worse = 0/25 = 0 Mean Score =					% B = 0/25 = % NC = 25/25 = 100 % W = 0/25 = MS =					% B = 0/25 = % NC = 25/25 = 100 % W = 0/25 = MS =					% B = 0/25 = % NC = 25/25 = 100 % W = 0/25 = MS =					% B = 1/25 = 4 % NC = 24/25 = 96 % W = 0/25 = 0 MS =					

	4.5 hr					5.5 hr					8 hr					8.5 hr					12 hr					12.5 hr					
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	
4																														4
3																														3
2																														2
1						1					1						1									1					1
0	25					24					24						24				25					24					0
-1																														-1
-2																														-2
-3																														-3
-4																														-4
	% B = 0/25 = % NC = 25/25 = 100 % W = 0/25 = MS =					% B = 1/25 = 4 % NC = 24/25 = 96 % W = 0/25 = 0 MS =					% B = 1/25 = 4 % NC = 24/25 = 96 % W = 0/25 = 0 MS =					% B = 1/25 = 4 % NC = 24/25 = 96 % W = 0/25 = 0 MS =					% B = 0/25 = % NC = 25/25 = 100 % W = 0/25 = MS =					% B = 1/25 = 4 % NC = 24/25 = 96 % W = 0/25 = 0 MS =					

BEI 1025 C

Table 4. Initial summation of data recorded on Form 3

Which symptom is recoded below (Circle one); Stuffy Nose, Runny Nose, Sneezing, Itching (Eyes, Nose), (Coughing), Muscle Ache

Data pertains to (Ck appropriate squares): ☐ Group 1; ☒ Group 2; ☐ Placebo; ☒ Active.

0 hr

	0	No	2	3	4
4		0		4	0
3		3		3	9
2		12		2	24
1		10		1	10
0		0		0	0
-1	Sum	25			43

Initial Mean Score = $\frac{43}{25}$ = 1.72

1/4 hr

	0	1	2	3	4
4					
3					
2					
1		1			
0		6	11	3	
-1		3	1		

% Better = 1/25 = 4
% No Chg = 20/25 = 80
% Worse = 4/25 = 16
Mean Score = $\frac{1-0-4}{25}$ = −0.12

1/2 hr

	0	1	2	3	4
4					
3					
2					
1		2		1	
0		5	11		
-1		3	1	2	

% B = 3/25 = 12
% NC = 16/25 = 64
% W = 6/25 = 24
MS = $\frac{3-6}{25}$ = −0.12

1 hr

	0	1	2	3	4
4					
3					
2		1	1		
1		4	4	2	
0		5	7		
-1				1	

% B = 12/26 = 48
% NC = 12/25 = 48
% W = 1/25 = 4
MS = (4+10−1)/25 = 0.52

2 hr

	0	1	2	3	4
4					
3					
2		1	1		
1		3	4	1	
0		6	7	1	
-1				1	

% B = 10/25 = 40
% NC = 14/25 = 56
% W = 1/25 = 4
MS = (4+8−1)/25 = 0.44

4 hr

	0	1	2	3	4
4					
3					
2		1			
1		2	3	1	
0		7	9	2	
-1					

% B = 7/25 = 28
% NC = 18/25 = 72
% W = 0/25 = 0
MS = (2+6)/25 = 0.32

4.5 hr

	0	1	2	3	4
4					
3					
2		1	2	2	
1		1	5		
0		8	5	1	
-1					

% B = 11/25 = 44
% NC = 14/25 = 56
% W = 0/25 = 0
MS = (0+6)/25 = 0.64

5.5 hr

	0	1	2	3	4
4					
3					
2		1	3	1	
1		3	1	1	
0		5	3	1	
-1		1			

% B = 10/25 = 40
% NC = 14/25 = 56
% W = 1/25 = 4
MS = (0+5−1)/25 = 0.56

8 hr

	0	1	2	3	4
4					
3					
2		1			
1		3	6	2	
0		6	6	1	
-1					

% B = 12/25 = 48
% NC = 13/25 = 52
% W = 0/25 = 0
MS = (2+11)/25 = 0.52

8.5 hr

	0	1	2	3	4
4					
3					
2				1	
1		5	3	1	
0		5	9		
-1				1	

% B = 10/25 = 40
% NC = 14/25 = 56
% W = 1/25 = 4
MS = (2+9−1)/25 = 0.40

12 hr

	0	1	2	3	4
4					
3					
2		1			
1			2	2	
0		9	10	1	
-1					

% B = 5/25 = 20
% NC = 20/25 = 80
% W = 0/25 = 0
MS = (2+4)/25 = 0.24

12.5 hr

	0	1	2	3	4
4					
3					
2					
1		3	4	2	
0		7	8	1	
-1					

% B = 9/25 = 36
% NC = 16/25 = 64
% W = 0/25 = 0
MS = 9/25 = 0.36

BEI 1025 a

Table 4. Initial summation of data recorded on Form 3

Which symptom is recoded below (Circle one); Stuffy Nose, Runny Nose, Sneezing, Itching (Eyes, Nose), Coughing, (Muscle Ache)

Data pertains to (Ck appropriate squares): ☐ Group 1; ☒ Group 2; ☐ Placebo; ☒ Active.

	0 hr					1/4 hr					1/2 hr					1 hr					2 hr					4 hr					
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	
4		0		4	0																									4
3		0		3	0																									3
2		9		2	18																									2
1		14		1	14												1	2				2	3				2	1		1
0		2		0	0	2	12	9			2	13	9			2	13	7			2	11	6			2	12	3			0
-1	Sum:	25			32		2					1										1									-1
-2																															-2
-3																															-3
-4																															-4
	Initial Mean Score = 32/25 = 1.28 (1.39)					% Better = 0/25 = 0%; % No Chg. = 23/25 = 92%; % Worse = 2/25 = 8%; Mean Score = −2/25 = −0.08 (%B=0.0; MS=−0.07)					% B = 0/25 = 0%; % NC = 23/25 = 92%; % W = 1/25 = 4%; MS = −1/25 = −0.04 (%B=0; MS=−0.04)					% B = 3/25 = 12%; % NC = 22/25 = 88%; % W = 0/25 = 0%; MS = 3/25 = 0.12 (%B=13; MS=0.13)					% B = 5/25 = 20%; % NC = 17/25 = 68%; % W = 1/25 = 4%; MS = 5/25 = 0.20 (%B=22; MS=0.17)					% B = 3/25 = 12%; % NC = 22/25 = 88%; % W = 0/25 = 0%; MS = 3/25 = 0.12 (%B=13; MS=0.13)				

	4.5 hr					5.5 hr					8 hr					8.5 hr					12 hr					12.5 hr					
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	
4																															4
3																															3
2		1					1	1																							2
1		1	1				1	2				4	3				3	4				3					3	3			1
0	2	12	9			2	12	6			2	9	6			2	11	5			2	11	9			2	11	6			0
-1												1																			-1
-2																															-2
-3																															-3
-4																															-4
	% B = 3/25 = 12%; % NC = 22/25 = 88%; % W = 0/25 = 0%; MS = 2+2/25 = 0.16 (%B=13; MS=0.17)					% B = 5/25 = 20%; % NC = 20/25 = 80%; % W = 0/25 = 0%; MS = 4+3/25 = 0.28 (%B=22; MS=0.30)					% B = 7/25 = 28%; % NC = 17/25 = 68%; % W = 1/25 = 4%; MS = 7−1/25 = 0.24 (%B=30; MS=0.26)					% B = 7/25 = 28%; % NC = 18/25 = 72%; % W = 0/25 = 0%; MS = 7/25 = 0.28 (%B=30; MS=0.30)					% B = 3/25 = 12%; % NC = 22/25 = 88%; % W = 0/25 = 0%; MS = 3/25 = 0.12 (%B=13; MS=0.13)					% B = 6/25 = 24%; % NC = 19/25 = 76%; % W = 0/25 = 0%; MS = 6/25 = 0.24 (%B=26; MS=0.26)				

BEI 1025b

Table 5. Initial summation of data recorded on Form 3

Which symptom is recoded below (Circle one); (Stuffy Nose), Runny Nose, Sneezing, Itching (Eyes, Nose), Coughing, Muscle Ache

Data pertains to (Ck appropriate squares): ☒ Group 1; ☐ Group 2; ☒ Placebo; ☐ Active.

Scale	0 hr					1/4 hr					1/2 hr					1 hr					2 hr					4 hr				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4		0		4	0																									
3		13		3	39																									
2		62		2	124								1					6	2				2	1					
1		0		1	0			2	1				23	6				33	10				43	10				30	7	
0		0		0	0			99	10				34	5				18	1				15	2				29	5	
-1	5	75			43			1	2				4	2				5					2					3	1	
-2																														
-3																														
-4																														

Initial Mean score = 143/75 = 2.17

% Better = 3/75 = 4.0
% No Chg. = 69/75 = 92.0
% Worse = 3/75 = 4.0
Mean score = (3-3)/75 = 0.0

% B = 30/75 = 40
% NC = 39/75 = 52
% W = 6/75 = 8
MS = (2+29-4)/75 = 0.33

% B = 51/75 = 68
% NC = 19/75 = 25
% W = 5/75 = 7
MS = (24+43-5)/75 = 0.83

% B = 56/75 = 75
% NC = 17/75 = 23
% W = 2/75 = 3
MS = (6+53-2)/75 = 0.76

% B = 37/75 = 49
% NC = 34/75 = 45
% W = 4/75 = 6
MS = (37-4)/75 = 0.44

Scale	4.5 hr					5.5 hr					8 hr					8.5 hr					12 hr					12.5 hr				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4																														
3																														
2			7					7	1									6	1									3	1	
1			45	12				32	9				29	9				35	8				29	10				31	9	
0			8	1				20	3				31	4				21	4				31	3				24	2	
-1			2					3					2											2				4	1	
-2																														
-3																														
-4																														

% B = 64/75 = 85
% NC = 9/75 = 12
% W = 2/75 = 3
MS = (14+57-2)/75 = 0.72

% B = 49/75 = 65
% NC = 23/75 = 31
% W = 3/75 = 4
MS = (16+41-3)/75 = 0.72

% B = 38/75 = 51
% NC = 35/75 = 47
% W = 2/75 = 3
MS = (38-2)/75 = 0.48

% B = 50/75 = 67
% NC = 25/75 = 33
% W = 0/75 = 0
MS = (14+43)/75 = 0.75

% B = 39/75 = 52
% NC = 34/75 = 45
% W = 2/75 = 3
MS = (39-2)/75 = 0.49

% B = 44/75 = 59
% NC = 26/75 = 34
% W = 5/75 = 7
MS = (8+40-5)/75 = 0.57

BEI 1025b

Table 5. Initial summation of data recorded on Form 3

Which symptom is recoded below (Circle one); Stuffy Nose, (Runny Nose) Sneezing, Itching (Eyes, Nose), Coughing, Muscle Ache

Data pertains to (Ck appropriate squares): ☒ Group 1; ☐ Group 2; ☒ Placebo; ☐ Active.

	0 hr			Score		1/4 hr					1/2 hr					1 hr					2 hr					4 hr					
	0	No	2			0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	
4		0		4	0																										4
3		9		3	27																										3
2		63		2	126								1				1	7	1				4	1			1				2
1		3		1	3			2				2	21	6			2	37	7			3	31	5			2	23	4		1
0		0		0	0		3	56	8			1	28	2				13					25	3			1	35	3		0
-1		10						3	1				3	1				6	1				3					4	2		-1
-2					156																										-2
-3																															-3
-4																															-4

Initial Mean Score = $\frac{156}{75}$ = 2.08

% Better = 2/75 = 3
% No Chg = 69/75 = 92
% Worse = 4/75 = 5
Mean score = (2-4)/75 = -0.03

% B = 30/75 = 40
% NC = 41/75 = 55
% W = 4/75 = 5
MS = (2+29-4)/75
0.36

% B = 55/75 = 73
% NC = 13/75 = 17
% W = 7/75 = 10
MS = (18+46-7)/75
0.76

% B = 44/75 = 59
% NC = 28/75 = 37
% W = 3/75 = 4
MS = (10+39-3)/75
0.61

% B = 30/25 = 40
% NC = 39/75 = 52
% W = 6/75 = 8
MS = (2+29-6)/75
0.33

	4.5 hr					5.5 hr					8 hr					8.5 hr					12 hr					12.5 hr					
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	
4																															4
3																												1			3
2			10	1			1	6					2					6					2					3			2
1		1	32	5			1	36	6			2	22	5			2	33	5			2	23	4			2	27	5		1
0		1	19	3			1	19	3			1	36	4			1	22	4				37	5			1	31	4		0
-1		1	2					2					3					2				1	1					1			-1
-2																															-2
-3																															-3
-4																															-4

% B = 49/75 = 65
% NC = 23/75 = 31
% W = 3/75 = 4
MS = (22+39-5)/75
0.76

% B = 50/75 = 67
% NC = 23/75 = 31
% W = 2/75 = 2
MS = (14+43-2)/75
= 0.73

% B = 31/75 = 41
% NC = 41/75 = 55
% W = 3/75 = 4
MS = (4+29-3)/75
0.37

% B = 46/75 = 61
% NC = 27/75 = 36
% W = 2/75 = 3
MS = (12+40-2)/75
0.67

% B = 31/75 = 41
% NC = 42/75 = 56
% W = 2/75 = 3
MS = (4+29-2)/75
0.41

% B = 38/75 = 51
% NC = 36/75 = 48
% W = 1/75 = 1
MS = (3+6+34-1)/75
0.56

BEI 1025b

Table 5. Initial summation of data recorded on Form 3

Which symptom is recoded below (Circle one); Stuffy Nose, Runny Nose, (Sneezing) Itching (Eyes, Nose), Coughing, Muscle Ache

Data pertains to (Ck appropriate squares): ☒ Group 1; ☐ Group 2; ☒ Placebo; ☐ Active.

	0 hr					1/4 hr					1/2 hr					1 hr					2 hr					4 hr				
	0	½	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4		0		4													1					1					1				
3		4		5	12												1					1					1				
2		14		3	22							1	1				3	7				2	5				2	4			
1		28		1	25		3	7	2			6	17	1			14	20	2			13	19	1			10	13			
0		3		0	0	2	18	27	2		1	10	14	3		1	5	6	1		2	7	13	3		2	9	17	4		
-1	Sum	51			122		7	7			1	10	9			1	4	8	1			3	5				5	7			
-2												1																			
-3																														
-4																														

Initial Mean Score = 122/75 = 1.68

% Better = 12/73 = 16
% No chg. = 47/73 = 64
% Worse = 14/73 = 19
Mean Score = (52−14)/73 = 0.05

% B = 26/73 = 36
% NC = 37/73 = 51
% W = 20/73 = 27
MS = (2+24−19−2)/73 = 0.07

% B = 48/73 = 66
% NC = 13/73 = 18
% W = 13/73 = 18
MS = (4+3+20+36−7)/73 = 0.68

% B = 42/73 = 58
% NC = 23/73 = 31
% W = 8/73 = 11
MS = (4+3+14+33−8)/73 = 0.68

% B = 31/73 = 43
% NC = 30/73 = 41
% W = 12/73 = 16
MS = (4+3+12+23−12)/73 = 0.41

	4.5 hr					5.5 hr					8 hr					8.5 hr					12 hr					12.5 hr				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4							1										1	1					1					1			
3		1	1					3															1				1	2			
2		6	4				5	6				3	2				4	9				2	3				5	5			
1		15	11	1			13	13	2			9	13	2			10	15				10	12	1			12	17			
0	1	3	15	3		1	5	14	2		1	6	19	2		2	7	12	3		2	11	19	3		2	7	14	4		
-1	1	2	5			1	4	4			1	10	7				6	4	1			5	5				3	2			
-2								1																						
-3																														
-4																														

% B = 45/73 = 62
% NC = 21/73 = 29
% W = 7/73 = 9
MS = (6+30+28−7)/73 = 0.78

% B = 43/73 = 59
% NC = 23/73 = 32
% W = 7/73 = 10
MS = (4+9+22+28−8−2)/73 = 0.73

% B = 29/73 = 40
% NC = 27/73 = 37
% W = 17/73 = 23
MS = (10+24−17)/73 = 0.70

% B = 40/73 = 55
% NC = 22/73 = 30
% W = 11/73 = 15
MS = (8+26+15−11)/73 = 0.52

% B = 30/73 = 41
% NC = 33/73 = 45
% W = 10/73 = 14
MS = (4+3+10+23−14)/73 = 0.41

% B = 43/73 = 60
% NC = 25/73 = 34
% W = 5/73 = 7
MS = (4+9+20−5)/73 = 0.38

BEI 1025b

Table 5. Initial summation of data recorded on Form 3

Which symptom is recoded below (Circle one); Stuffy Nose, Runny Nose, Sneezing, Itching (Eyes, Nose) Coughing, Muscle Ache

Data pertains to (Ck appropriate squares): ☒ Group 1; ☐ Group 2; ☒ Placebo; ☐ Active.

	0 hr Score					1/4 hr					1/2 hr					1 hr					2 hr					4 hr				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4		0		4	0																									
3		0		3	0																									
2		0		2	0																									
1		3		1	3																									
0		72		0	0	72	3				72	3				72	3				72	3				72	3			
-1	Sum	75																												
-2																														
-3																														
-4																														

Initial Mean Score

% Better = 0/75 =
% Nochg. = 75/75 =
% Worse = 0/75 =
Mean Score =

% B = 0/75 =
% NC = 75/75 =
% W = 0/75 =
MS =

% B = 0/75 =
% NC = 75/75 =
% W = 0/75 =
MS =

% B = 0/75 =
% NC = 75/75 =
% W = 0/75 =
MS =

% B = 0/75 =
% NC = 75/75 =
% W = 0/75 =
MS =

	4.5 hr					5.5 hr					8 hr					8.5 hr					12 hr					12.5 hr				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4																														
3																														
2																														
1												3					1					1					1			
0	72	3				72	3				72					72	2				72	2				72	2			
-1																														
-2																														
-3																														
-4																														

% B = 0/75 =
% NC = 75/75 =
% W = 0/75 =
MS =

% B = 0/75 =
% NC = 75/75 =
% W = 0/75 =
MS =

% B = 3/75 =
% NC = 72/75 =
% W = 0/75 =
MS =

% B = 1/75 =
% NC = 74/75 =
% W = 0/75 =
MS =

% B = 1/75 =
% NC = 74/75 =
% W = 0/75 =
MS =

% B = 1/75 =
% NC = 74/75 =
% W = 0/75 =
MS =

BEI 1025b

Table 5. Initial summation of data recorded on Form 3

Which symptom is recoded below (Circle one); Stuffy Nose, Runny Nose, Sneezing, Itching (Eyes, Nose), (Coughing), Muscle Ache

Data pertains to (Ck appropriate squares): ☒ Group 1; ☐ Group 2; ☒ Placebo; ☐ Active.

	0 hr Score					1/4 hr					1/2 hr					1 hr					2 hr					4 hr					
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	
4		0		4	0																									4
3		4		3	12																									3
2		29		2	58													1												2
1		40		1	40		1					6	6	2			7	6	2			11	8	2			7	8			1
0		2		0	0	2	35	27	4		2	27	21	2		2	31	20	2		2	25	21	2		2	29	22	4		0
-1	Rem	73			110		14	22				7	2				2	2				3	1				3				-1
-2																															-2
-3																															-3
-4																															-4

Initial Mean Score = 110/73 = 1.51

% Better = 1/73 = 1
% No Chg. = 64/73 = 91
% Worse = 6/73 = 8
Mean Score (7-6)/73 = -0.06

% B = 14/73 = 19
% NC = 50/73 = 68
% W = 9/73 = 13
MS: (14-9)/73 = -0.07

% B = 16/73 = 22
% NC = 53/73 = 73
% W = 4/73 = 5
MS = (2+15-4)/73 = 0.18

% B = 21/73 = 29
% NC = 48/73 = 66
% W = 4/73 = 5
MS = (21-4)/73 = 0.23

% B = 15/73 = 21
% NC = 55/73 = 75
% W = 3/73 = 4
MS = (15-3)/73 = 0.16

	4.5 hr					5.5 hr					8 hr					8.5 hr					12 hr					12.5 hr					
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	
4																														4
3																														3
2		2	1				1	2					1					1					1					1			2
1		4	10	2			12	15				7	8				12	9	1			7	7				7	8	1		1
0	2	53	17	2		2	27	12	4		2	31	20	4		2	28	18	3		2	32	21	4		2	33	16	3		0
-1		2	1									2						1				1					4			-1
-2																														-2
-3																														-3
-4																														-4

% B = 19/73 = 26
% NC = 51/73 = 69
% W = 3/73 = 5
MS = (6+16-3)/73 = 0.26

% B = 30/73 = 41
% NC = 43/73 = 59
% W = 0/73 = 0
MS = (6+27)/73 = 0.45

% B = 16/73 = 22
% NC = 57/73 = 75
% W = 2/73 = 3
MS = (2+15-2)/73 = 0.21

% B = 23/73 = 32
% NC = 49/73 = 67
% W = 1/73 = 1
MS = (2+22-1)/73 = 0.32

% B = 15/73 = 21
% NC = 57/73 = 78
% W = 1/73 = 1
MS = (2+14-1)/73 = 0.21

% B = 17/73 = 23
% NC = 52/73 = 71
% W = 4/73 = 6
MS = (2+16-4)/73 = 0.19

BEI 1025b

Table 5. Initial summation of data recorded on Form 3

Which symptom is recoded below (Circle one); Stuffy Nose, Runny Nose, Sneezing, Itching (Eyes, Nose), Coughing, (Muscle Ache)

Data pertains to (Ck appropriate squares): ☒ Group 1; ☐ Group 2; ☒ Placebo; ☐ Active.

	0 hr					1/4 hr					1/2 hr					1 hr					2 hr					4 hr					
	0	1/6	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	
4		0		4	0																										4
3		0		3	0																										3
2		16		2	32																										2
1		50		1	50				3	4							6	2				8	8				3	4			1
0		9		0	0	9	147	16			9	46	12			9	43	12			9	40	8			9	42	12			0
-1	Sum	25			82		3					1					1	2				2					3	2			-1
-2																															-2
-3																															-3
-4																															-4
	Initial Mean Score = 82/66 = 1.24					% Better = 0/66 = 0 % No Chg. = 63/66 = 95 % Worse = 3/66 = 5 Mean Score = (-3)/66 -0.05					% B = 7/66 = 11 % NC = 58/66 = 88 % W = 1/66 = 1 MS = (7-1)/66 0.09					% B = 8/66 = 12 % NC = 55/66 = 83 % W = 3/66 = 5 MS = (8-3)/66 0.08					% B = 16/66 = 24 % NC = 48/66 = 73 % W = 2/66 = 3 MS = (16-2)/66 0.21					% B = 7/63 = 11 % NC = 54/66 = 82 % W = 3/66 = 7 MS = (7-5)/66 0.03					

	4.5 hr					5.5 hr					8 hr					8.5 hr					12 hr					12.5 hr					
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	
4																															4
3																															3
2			1				1	1					1					1					1					1			2
1		7	7				8	6				7	4				7	4				4	1				8	3			1
0	9	40	9			9	39	8			9	42	10			9	40	11			9	43	14			9	40	12			0
-1		2					2					1	1				3					3					2				-1
-2								1																							-2
-3																															-3
-4																															-4
	% B = 15/66 = 23 % NC = 49/66 = 74 % W = 2/66 = 3 MS = (23-2)/66 0.21					% B = 16/66 = 24 % NC = 47/66 = 71 % W = 3/66 = 5 MS = (4+14-2-2)/66 0.21					% B = 12/66 = 18 % NC = 53/66 = 79 % W = 2/66 = 3 MS = (2+11-2)/66 0.17					% B = 12/66 = 18 % NC = 51/66 = 77 % W = 3/66 = 5 MS = (2+11-3)/66 0.15					% B = 6/66 = 9 % NC = 57/66 = 86 % W = 3/66 = 5 MS = (2+5-3)/66 0.06					% B = 12/66 = 18 % NC = 52/66 = 79 % W = 2/66 = 3 MS = (2+11-2)/66 0.17					

Table 5. Initial summation of data recorded on Form 3

Which symptom is recoded below (Circle one); (Stuffy Nose), Runny Nose, Sneezing, Itching (Eyes, Nose), Coughing, Muscle Ache

Data pertains to (Ck appropriate squares): ☐ Group 1; ☒ Group 2; ☐ Placebo; ☒ Active.

	0 hr					1/4 hr					1/2 hr				
	0	N	2	3	4	0	1	2	3	4	0	1	2	3	4
4		2		4	8										
3		16		3	48										
2		56		2	112					1			4	2	1
1		1		1	1			2	2				27	10	
0		0		0	0		1	52	11	1		1	24	4	1
-1		75			169			1					1		
-2								1							
-3															
-4															
	Initial Mean Score = 169/75 = 2.25					%Better = 5/75 = 7; %No Chg = 68/75 = 90; %Worse = 2/75 = 3; Mean Score = (2+4-1-2)/75 = 0.04					%B = 44/75 = 59; %NC = 30/75 = 40; %W = 1/75 = 1; MS = (74-1)/75 = 0.97				

	1 hr					2 hr					4 hr					
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	
																4
								4						1		3
			21	5				14	6				4			2
		1	30	10			1	29	10	1			34	11	1	1
			3	1	1			9		1		1	17	3	1	0
			2		1								1	1		-1
																-2
																-3
																-4
	%B = 67/75 = 89; %NC = 5/75 = 7; %W = 3/75 = 4; MS = (52+41-3)/75 = 1.20					%B = 65/75 = 87; %NC = 10/75 = 13; %W = 0/75 = 0; MS = (12+40+41)/75 = 1.24					%B = 51/75 = 68; %NC = 22/75 = 29; %W = 2/75 = 3; MS = (3+8+46)/75 = 0.76					

	4.5 hr					5.5 hr					8 hr				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4															
3			2	1				3	1						
2			15	3				20	7				8	3	1
1			20	10	2			26	8	1		1	31	8	
0		1	10	2			1	7		1			15	5	1
-1													2		
-2															
-3															
-4															
	%B = 62/75 = 83; %NC = 13/75 = 17; %W = 0/75 = 0; MS = (12+52+42)/75 = 1.15					%B = 66/75 = 88; %NC = 9/75 = 12; %W = 0/75 = 0; MS = (12+54+35)/75 = 1.35					%B = 52/75 = 69; %NC = 21/75 = 28; %W = 2/75 = 3; MS = (24+40-2)/75 = 0.82				

	8.5 hr					12 hr					12.5 hr					
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	
																4
			2					1					1	1		3
			17	4				3	3	1			16	7		2
		1	28	11	1			38	9	1			34	6	1	1
			7	2	1		1	12	3			1	5	1	1	0
			1					2	1				1			-1
																-2
																-3
																-4
	%B = 64/75 = 85; %NC = 10/75 = 13; %W = 1/75 = 2; MS = (6+42+41)/75 = 1.17					%B = 56/75 = 75; %NC = 16/75 = 21; %W = 3/75 = 4; MS = (3+20+48-3)/75 = 0.91					%B = 66/75 = 88; %NC = 8/75 = 11; %W = 1/75 = 1; MS = (6+46+41-1)/75 = 1.23					

BEI 1025b

Table 5. Initial summation of data recorded on Form 3

Which symptom is recoded below (Circle one); Stuffy Nose, (Runny Nose), Sneezing, Itching (Eyes, Nose), Coughing, Muscle Ache

Data pertains to (Ck appropriate squares): ☐ Group 1; ☒ Group 2; ☐ Placebo; ☒ Active.

Score	0 hr	1/4 hr	1/2 hr	1 hr	2 hr	4 hr
4	0					
3	16			1	3 1	1
2	58		7 2	19 7	15 6	4 1
1	1	3 4	26 7	1 32 6	1 32 6	35 6
0	0	1 54 12	1 24 6	4 3	7 3	1 18 6
-1	Sum 75	1	1 1	2	1	1 2
		166				
	Initial Mean Score = 145/75 = 2.20	%B = 7/75 = 9 %NC = 67/75 = 90 %W = 1/75 = 1 Mean Score = (7-1)/75 = 0.09	%B = 42/75 = 56 %NC = 31/75 = 41 %W = 2/75 = 3 MS = (18+33-2)/75 = 0.65	%B = 66/75 = 88 %NC = 7/75 = 9 %W = 2/75 = 3 MS = (3+52+39-2)/75 = 1.23	%B = 64/75 = 85 %NC = 10/75 = 14 %W = 1/75 = 1 MS = (12+42-1)/75 = 0.71	%B = 47/75 = 63 %NC = 25/75 = 33 %W = 3/75 = 4 MS = (3+10+41-3)/75 = 0.68

Score	4.5 hr	5.5 hr	8 hr	8.5 hr	12 hr	12.5 hr
4						
3	2 2	4 1		2		2
2	18 5	20 8	8 4	16 7	13 2	20 5
1	28 8	25 6	34 8	1 32 5	26 9	1 31 8
0	1 10 1	1 6 1	1 16 4	8 3	1 18 4	5 3
-1				1	1 1	
	%B = 93/75 = 94 %NC = 12/75 = 16 %W = 0/75 = 0 MS = (12+46+36)/75 = 1.25	%B = 67/75 = 89 %NC = 8/75 = 0 %W = 8/75 = 0 MS = (15+56+36)/75 = 1.43	%B = 54/75 = 72 %NC = 21/75 = 28 %W = 0/75 = 0 MS = (24+42)/75 = 0.88	%B = 93/75 = 94 %NC = 1/75 = 1 %W = 1/75 = 1 MS = (6+46+38-1)/75 = 1.19	%B = 50/75 = 67 %NC = 23/75 = 31 %W = 2/75 = 2 MS = (30+35-2)/75 = 0.84	%B = 67/75 = 89 %NC = 8/75 = 0 %W = 0/75 = 0 MS = (6+50+40)/75 = 1.28

BEI 1025b

Table 5. Initial summation of data recorded on Form 3

Which symptom is recoded below (Circle one); Stuffy Nose, Runny Nose, (Sneezing), Itching (Eyes, Nose), Coughing, Muscle Ache

Data pertains to (Ck appropriate squares): ☐ Group 1; ☒ Group 2; ☐ Placebo; ☒ Active.

Score	0 hr	1/4 hr	1/2 hr	1 hr	2 hr	4 hr
4	0	1		1	2	
3	4			5	6	1
2	52		2 8 1	5 17 1	3 17 1	2 8
1	11	6 1	9 26 2	11 23 2	12 19 2	10 23 2
0	0	17 30 2	5 12	3 4	1 7 1	6 16 1
-1	135	2 15 1	3 6 1	2 1	1 1	2 3 1
-2						
-3						
-4						
Mean Score	135/75 = 1.80					
		%Better = 5/75 = 11 %No Chg = 49/75 = 65 %Worse = 18/75 = 24 Mean Score = (4+7-18)/75 = -0.20	%B = 48/75 = 64 %NC = 17/75 = 23 %W = 10/75 = 13 MS = (22+37-10)/75 = 0.65	%B = 65/75 = 87 %NC = 7/75 = 9 %W = 3/75 = 4 MS = (4+15+36-3)/75 = 0.69	%B = 64/75 = 85 %NC = 9/75 = 12 %W = 2/75 = 3 MS = (8+24+42-33-2)/75 = 1.40	%B = 46/75 = 61 %NC = 23/75 = 31 %W = 6/75 = 8 MS = (3+20+35-6)/75 = 0.69

Score	4.5 hr	5.5 hr	8 hr	8.5 hr	12 hr	12.5 hr
4	1	1	1		1	2
3	2 6 1	2 11 1	1 1	2 5	1	8 1
2	4 16 1	4 17 2	2 15	4 18	3 12	9 14 1
1	9 2	12 16 1	10 21 2	8 25 2	9 17 3	8 24 1
0	1 7	7	4 9 1	2 3 2	5 1 1	2 3 1
-1	3 1	1	2 5	3 1	2 8	1
-2						
-3						
-4						
	%B = 61/75 = 81 %NC = 10/75 = 13 %W = 4/75 = 6 MS = (4+27+42+30-4)/75 = 1.32	%B = 67/75 = 89 %NC = 7/75 = 9 %W = 1/75 = 2 MS = (4+42+46+29-1)/75 = 1.60	%B = 53/75 = 71 %NC = 15/75 = 20 %W = 7/75 = 9 MS = (4+6+33-7)/75 = 0.48	%B = 64/75 = 85 %NC = 7/75 = 9 %W = 4/75 = 6 MS = (2+44+35-4)/75 = 1.28	%B = 52/75 = 69 %NC = 13/75 = 17 %W = 10/75 = 14 MS = (4+21+29-10)/75 = 0.59	%B = 68/75 = 91 %NC = 6/75 = 8 %W = 1/75 = 1 MS = (8+27+48+33-1)/75 = 1.53

BEI 1025b

Table 5. Initial summation of data recorded on Form 3

Which symptom is recoded below (Circle one); Stuffy Nose, Runny Nose, Sneezing, (Itching (Eyes, Nose)), Coughing, Muscle Ache

Data pertains to (Ck appropriate squares): ☐ Group 1; ☒ Group 2; ☐ Placebo; ☒ Active.

	0 hr					1/4 hr					1/2 hr					1 hr					2 hr					4 hr				
	0	No	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4		0																												
3		0																												
2		0																												
1		3		1			1				1	1				1	2				1	3					2			
0		72				72	2				71	2				71	1				71					72	1			
-1																														
-2																														
-3																														
-4																														

	4.5 hr					5.5 hr					8 hr					8.5 hr					12 hr					12.5 hr				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4																														
3		1					1					1					1										1			
2																						1					1			
1		1					1				1	2				2	1				1	1				1				
0	72	1				72	1				71					70	1				71	1				72	1			
-1																														
-2																														
-3																														
-4																														

BEF 1025b

Table 5 Summation of data from Table 4 BEF 1025a and Table 4 BEF 1025b giving subjective evaluation made by 200 patients (100 active, 100 placebo) of their relief from the symptoms of stuffy nose, runny nose, sneezing, coughing, and muscle ache following the oral administration of phenylephrine HCl tablets (5 mg) or placebo tablets.

Which symptom is recoded below (Circle one); (Stuffy Nose) Runny Nose, Sneezing, Itching (Eyes, Nose), Coughing, Muscle Ache

Data pertains to (Ck appropriate squares): ☒ Group 1; ☐ Group 2; ☒ Placebo; ☐ Active.

	0 hr Score					1/4 hr					1/2 hr					1 hr					2 hr					4 hr				
	0	No.	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4		1		4	4																									
3		20		3	60																									
2		79		2	158								1																	
1		0		1	0			3	1				29	7				7	2				5	1					1	
0		0		0	0			74	17	1			44	10	1			42	20				52	13	1			39	10	
-1		100		Sum	222			2	2				5	3				21	1	1			19	6				36	8	1
-2																		6					3					4	1	
-3																														
-4																														

Initial Mean Score = 2.22

%B = 4
%NC = 92
%W = 4
MS = (4-4)/100
0.0

%B = 37
%NC = 55
%W = 8
MS = (2+36-8)/100
0.30

%B = 71
%NC = 23
%W = 6
MS = (18+62-6)/100
0.74

%B = 72
%NC = 25
%W = 3
MS = (12+66-3)/100
0.75

%B = 50
%NC = 45
%W = 5
MS = (2+49-5)/100
0.46

	4.5 hr					5.5 hr					8 hr					8.5 hr					12 hr					12.5 hr				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4																														
3																														
2			7	1				7	1									7	1									3	1	
1			54	16	1			46	14				36	13				46	12	1			39	13				32	10	
0			13	3				22	5	1			41	7				26	7				36	7				33	7	
-1			5					4					2		1								4		1			11	2	
-2																														1
-3																														
-4																														

%B = 39
%NC = 56
%W = 5
MS = (16+71-5)/100
0.82

%B = 68
%NC = 29
%W = 3
MS = (16+60-4)/100
0.72

%B = 48
%NC = 49
%W = 3
MC = (49-3)/100
0.46

%B = 67
%NC = 33
%W = 0
MS = (66+59)/100
0.75

%B = 52
%NC = 43
%W = 5
MS = (52-5)/100
0.47

%B = 46
%NC = 40
%W = 14
MS = (8+42-13-2)/100
0.35

BEI 10255

Table 5. Initial summation of data recorded on Form 3

Which symptom is recoded below (Circle one); Stuffy Nose, Runny Nose, Sneezing, Itching (Eyes, Nose), (Coughing) Muscle Ache

Data pertains to (Ck appropriate squares): ☐ Group 1; ☒ Group 2; ☐ Placebo; ☒ Active.

	0 hr Score					1/4 hr					1/2 hr					1 hr					2 hr					4 hr					
	0	1/2	2	2½	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	
4		0		4	0												1					1					1				4
3		0		3	0																										3
2		3/2		2	6.4												2	1				1	1								2
1		1/3		1	43		1	1				4	8				18	12				12	14				7	7			1
0		0		0			36	30				34	22				26	19				29	16				32	25			0
-1	Sum	75			107		6	1				5	2				1						1				3				-1
-2																															-2
-3																															-3
-4																															-4
	Mean Score = 107/75 = 1.43					%B = 3/75 = 3 %NC = 58/75 = 77 %W = 7/75 = 9 Mean Score = (2−7)/75 = −0.07					%B = 12/75 = 16 %NC = 58/75 = 77 %W = 7/75 = 9 MS = (12−10)/75 = 0.03					%B = 29/75 = 39 %NC = 43/75 = 60 %W = 1/75 = 1 MS = (4+6+25−1)/75 = 0.55					%B = 29/75 = 39 %NC = 45/75 = 60 %W = 1/75 = 1 MS = (4+4+26−1)/75 = 0.44					%B = 15/75 = 20 %NC = 57/75 = 76 %W = 3/75 = 4 MS = (4+14−3)/75 = 0.20				

	4.5 hr					5.5 hr					8 hr					8.5 hr					12 hr					12.5 hr					
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	
4		1					1					1					1					1					1					4
3													1																		3
2		3	2				5	3									1	2				1	1					1			2
1		3	9				13	12				9	14				12	15				11	10				12	9			1
0		30	20				24	17				29	17				29	15				30	21				30	22			0
-1			1									4																			-1
-2																															-2
-3																															-3
-4																															-4
	%B = 24/75 = 32 %NC = 49/75 = 65 %W = 1/75 = 1 MS = (9+15+19−1)/75 = 0.41					%B = 24/75 = 32 %NC = 34/75 = 45 %W = 0/75 = 0 MS = (9+11+25)/75 = 0.60					%B = 25/75 = 33 %NC = 34/75 = 45 %W = 1/75 = 1 MS = (9+3+13−9)/75 = 0.21					%B = 31/75 = 41 %NC = 34/75 = 45 %W = 1/75 = 1 MS = (4+6+23)/75 = 0.47					%B = 24/75 = 32 %NC = 34/75 = 45 %W = 0/75 = 0 MS = (11+4+21)/75 = 0.39					%B = 23/75 = 31 %NC = 32/75 = 43 %W = 0/75 = 0 MS = (4+2+23)/75 = 0.36				

Table 5 Summation of data from Table 4 BEI 1025a and Table 4 BEI 1025b giving subjective evaluation made by 200 patients (100 active, 100 placebo) of their relief from the symptoms of stuffy nose, runny nose, sneezing, coughing, and muscle ache following the oral administration of phenylephrine HCl tablets (5 mg) or placebo tablets.

Which symptom is recoded below (Circle one); Stuffy Nose, Runny Nose, (Sneezing) Itching (Eyes, Nose), Coughing, Muscle Ache

Data pertains to (Ck appropriate squares): ☒ Group 1; ☐ Group 2; ☒ Placebo; ☐ Active.

	0 hr Score					1/4 hr					1/2 hr					1 hr					2 hr					4 hr				
	0	No.	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4		0		4	0												1					1					1			
3		7		3	21												2					2	1				1			
2		56		2	112							1	3				5	8	1			3	7				2	4	1	
1		35		1	35		4	10	2			9	28	3			17	30	3			16	27	3			13	16		
0		2		0	0	2	21	33	3		1	10	14	4		1	6	8	2		2	9	16	3		2	12	26	4	
-1		100		SUM	168		10	13	2		1	13	11	1		1	4	10	1			3	6	1			6	10	2	
-2												1																		
-3																														
-4																														

Initial Mean Score = 1.68

% Better = 16
% No Chg. = 57
% Worse = 22
Mean Score = (16-25)/100 = -0.09

% B = 44
% NC = 29
% W = 27
MS = (8+40-26-2)/100 = 0.20

% B = 67
% NC = 17
% W = 16
MS = (4+6+28+50-16)/100 = 0.72

% B = 60
% NC = 30
% W = 10
MS = (4+9+20+46-10)/100 = 0.69

% B = 38
% NC = 44
% W = 18
MS = (4+3+14+29-18)/100 = 0.32

	4.5 hr					5.5 hr					8 hr					8.5 hr					12 hr					12.5 hr				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4							1										1	1					1					1			
3		1	1					4										1					2					3			
2		17	10				6	7				3	2				5	9				2	4				1	6		
1		21	16	2			16	22	3			14	18	2			13	26				13	18	1			14	26	2	
0	1	4	12	5		1	5	17	3		1	8	25	3		2	10	15	5		2	13	23	5		2	10	17	5	
-1	1	2	10			1	7	5	1		1	10	11	2			6	4	2			7	8	1			3	3		
-2								1																						
-3																														
-4																														

% B = 58
% NC = 29
% W = 13
MS = (6+34+39-13)/100 = 0.66

% B = 59
% NC = 26
% W = 15
MS = (4+12+26+41-14-2)/100 = 0.67

% B = 39
% NC = 37
% W = 24
MS = (10+34-24)/100 = 0.20

% B = 56
% NC = 32
% W = 12
MS = (8+3+28+39-12)/100 = 0.66

% B = 41
% NC = 43
% W = 16
MS = (4+6+12+32-14)/100 = 0.38

% B = 60
% NC = 34
% W = 6
MS = (4+12+26+42-6)/100 = 0.78

1025b

Table 9. Summation of data from Table 4 BEI 1025a and Table 4 BEI 1025b giving subjective evaluation made by 200 patients (100 active, 100 placebo) of their relief from the symptoms of stuffy nose, runny nose, sneezing, coughing, and muscle ache following the oral administration of phenylephrine HCl tablets (5 mg) or placebo tablets.

Which symptom is recoded below (Circle one); Stuffy Nose, (Runny Nose) [circled], Sneezing, Itching (Eyes, Nose), Coughing, Muscle Ache

Data pertains to (Ck appropriate squares): [X] Group 1; [ ] Group 2; [X] Placebo; [ ] Active.

	0 hr			Score →		1/4 hr					1/2 hr					1 hr					2 hr					4 hr				
	0	No	2			0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4		0		4	0																									
3		16		3	48																									
2		81		2	162								2				1	8	2				4	2				1		
1		3		1	3			4				2	29	9			2	47	12			3	43	10			2	29	8	
0		0		0	0		3	74	15			1	47	3				20	1				31	4			1	47	5	
-1		100		SUM	213			3	1				4	3				6	1				3					4	3	
-2																														
-3																														
-4																														

Initial Mean Score = 2.13

1/4 hr: %Relief = 4; %No Chg = 92; %Worse = 4; Mean Score = (4−4)/100 = 0.00

1/2 hr: %B 42; %NC 51; %W 7; MS = (4+40−7)/100 = 0.37

1 hr: %B 72; %NC 21; %W 7; MS = (22+61−7)/100 = 0.76

2 hr: %B 62; %NC 35; %W 3; MS = (12+56−3)/100 = 0.65

4 hr: %B 40; %NC 53; %W 7; MS = (2+39−7)/100 = 0.34

	4.5 hr					5.5 hr					8 hr					8.5 hr					12 hr					12.5 hr				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4																														
3																												1		
2			10	3			1	7					2					8					2					4	1	
1		1	43	7			1	44	10			2	29	9			2	39	7			2	33	8			2	36	9	
0		1	24	5			1	27	6			1	46	6			1	32	9				43	7			1	39	5	
-1		1	4	1				3					4	1				2				1	3	1				1	1	
-2																														
-3																														
-4																														

4.5 hr: %B 64; %NC 30; %W 6; MS = (26+51−6)/100 = 0.71

5.5 hr: %B 63; %NC 34; %W 3; MS = (16+55−3)/100 = 0.68

8 hr: %B 42; %NC 53; %W 5; MS = (2+40−5)/100 = 0.37

8.5 hr: %B 56; %NC 42; %W 2; MS = (16+48−2)/100 = 0.62

12 hr: %B 45; %NC 50; %W 5; MS = (4+43−5)/100 = 0.42

12.5 hr: %B 53; %NC 45; %W 2; MS = (3+10+47−2)/100 = 0.58

1025b

Table 9. Summation of data from Table 4 BEI 1025a and Table 4 BEI 1025b giving subjective evaluation made by 200 patients (100 active, 100 placebo) of their relief from the symptoms of stuffy nose, runny nose, sneezing, coughing, and muscle ache following the oral administration of phenylephrine HCl tablets (5 mg) or placebo tablets.

Which symptom is recorded below (Circle one); Stuffy Nose, Runny Nose, Sneezing, Itching (Eyes, Nose), Coughing, Muscle Ache

Data pertains to (Ck appropriate squares): ☒ Group 1; ☐ Group 2; ☒ Placebo; ☐ Active.

	0 hr					1/4 hr					1/2 hr					1 hr					2 hr					4 hr				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4		0		4	0																									
3		0		5	0																									
2		0		2	0																									
1		4		1	4																									
0		96		0	0																									
		100			4																									

Initial Mean Score = 0.04

	4.5 hr					5.5 hr					8 hr					8.5 hr					12 hr					12.5 hr				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4																														
3																														
2																														
1																														
0																														

[illegible] 1025b

Table 9. Summation of data from Table 4 BEI 1025a and Table 4 BEI 1025b giving subjective evaluation made by 200 patients (100 active, 100 placebo) of their relief from the symptoms of stuffy nose, runny nose, sneezing, coughing, and muscle ache following the oral administration of phenylephrine HCl tablets (5 mg) or placebo tablets.

Which symptom is recoded below (Circle one); Stuffy Nose, Runny Nose, Sneezing, Itching (Eyes, Nose), Coughing, (Muscle Ache — circled)

Data pertains to (Ck appropriate squares): [X] Group 1; [ ] Group 2; [X] Placebo; [ ] Active.

	0 hr			Score		1/4 hr					1/2 hr				
	0	No.	2			0	1	2	3	4	0	1	2	3	4
4		0		4	0										
3		0		3	0										
2		22		2	44										
1		63		1	43							3	5		
0		15		0	0	15	40	22			15	59	17		
-1				SUM	107		3					1			
-2															
-3															
-4															
	Initial Mean Score = 1.07					% Better = 0 % No Change = 97 % W = 3 Mean Score = -3/100 -0.03					%B = 8 %NC = 91 %W = 1 MS = (8-1)/100 0.07				

	1 hr					2 hr					4 hr				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4															
3															
2															
1		7	2				11	9				3	5		
0	9	48	24	6		15	50	13			15	54	17		
-1		1	3				2					3	3		
-2															
-3															
-4															
	%B = 9 %NC = 87 %W = 4 MS = (9-4)/100 0.05					%B = 20 %NC = 78 %W = 2 MS = (20-2)/100 0.18					%B = 8 %NC = 86 %W = 6 MS = (8-6)/100 0.02				

	4.5 hr					5.5 hr					8 hr				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4															
3															
2			1				1	1					1		
1		11	7				10	7				10	5		
0	15	49	15			15	49	12			15	52	15		
-1		2					3	1				1	1		
-2								1							
-3															
-4															
	%B = 19 %NC = 79 %W = 2 MS = (2+18-2)/100 0.18					%B = 19 %NC = 76 %W = 5 MS = (4+17-4-2)/100 0.15					%B = 16 %NC = 82 %W = 2 MS = (2+15-2)/100 = 0.15				

	8.5 hr					12 hr					12.5 hr				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4															
3															
2			1					1					1		
1		9	7				4	3				8	4		
0	15	51	14			15	56	18			15	53	17		
-1		3					3					2			
-2															
-3															
-4															
	%B = 17 %NC = 80 %W = 3 MS = (2+16-3)/100 0.15					%B = 8 %NC = 89 %W = 3 MS = (2+7-3)/100 0.06					%B = 13 %NC = 85 %W = 2 MS = (2+12-2)/100 0.12				

(1025)

Table 9. Summation of data from Table 4 BEI 1025a and Table 4 BEI 1025b giving subjective evaluation made by 200 patients (100 active, 100 placebo) of their relief from the symptoms of stuffy nose, runny nose, sneezing, coughing, and muscle ache following the oral administration of phenylephrine HCl tablets (5 mg) or placebo tablets.

Which symptom is recoded below (Circle one); (Stuffy Nose) [circled], Runny Nose, Sneezing, Itching (Eyes, Nose), Coughing, Muscle Ache

Data pertains to (Ck appropriate squares): ☐ Group 1; ☒ Group 2; ☐ Placebo; ☒ Active.

	0 hr			Score		1/4 hr					1/2 hr					1 hr					2 hr					4 hr				
	0	No.	2	[illegible]	[illegible]	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4		2		4	8																									
3		21		3	63													1					4						1	
2		76		2	152					1			5	2	1			28	10				22	9				6		
1		1		1	1			3	2				35	14			1	42	10			1	40	12	1			48	16	1
0		0		0	[illegible]		1	71	19	1		1	34	5	1			3	1	1			10		1		1	21	3	1
-1		100		SUM	KAY			1					2					2		1								1	1	
-2		Calc. Mean Score		= 2.24				1																						
-3																														
-4																														

1/4 hr: %B. Hr = 6/100 = 6; %No Chg = 92/100 = 92; %W = 2/100 = 2; Mean Score = (2+5-1-2) = 0.04

1/2 hr: %B = 57; %NC = 41; %W = 2; MS = (16+49-2)/100 43/100 = 0.63

1 hr: %B = 92; %NC = 5; %W = 3; MS = (3+76+53-3)/100 = 1.29

2 hr: %B = 89; %NC = 11; %W = 0; MS = (12+62+54)/100 1.28

4 hr: %B = 72; %NC = 26; %W = 2; MS = (3+12+45-2)/100 0.78

	4.5 hr					5.5 hr					8 hr					8.5 hr					12 hr					12.5 hr				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4									1																					
3			3	2				3	1									4					1					3	1	
2			19	5				29	10				11	5	1			22	7				6	4	1			19	11	
1			40	12	2			37	9	1		1	42	11			1	36	13	1			54	13	1			49	7	1
0		1	14	2			1	7		1			21	5	1			12	2	1		1	13	3			1	5	1	1
-1													2					1					2	1				1		
-2																														
-3																														
-4																														

4.5 hr: %B = 83; %NC = 17; %W = 0; MS = (15+48+54)/100 1.17

5.5 hr: %B = 91; %NC = 9; %W = 0; +47; MS = (4+12+78)/100 1.41

8 hr: %B = 71; %NC = 27; %W = 2; MS = (34+54-2)/100 0.86

8.5 hr: %B = 84; %NC = 15; %W = 1; MS = (12+58+51-1)/100 1.20

12 hr: %B = 80; %NC = 17; %W = 3; MS = (3+22+68-3)/100 0.90

12.5 hr: %B = 91; %NC = 8; %W =; MS = (12+60+57-1)/100 1.28

BEI 1025 [illegible] 1025b

Table 9. [illegible]mmation of data from Table 4 BEI 1025a and Table 4 BEI 1025b giving subjective evaluation made by 200 patients (100 active, 100 placebo) of their relief from the symptoms of stuffy nose, runny nose, sneezing, coughing, and muscle ache following the oral administration of phenylephrine HCl tablets (5 mg) or placebo tablets.

Which symptom is recoded below (Circle one); Stuffy Nose, **(Runny Nose)** Sneezing, Itching (Eyes, Nose), Coughing, Muscle Ache

Data pertains to (Ck appropriate squares): ☐ Group 1; ☒ Group 2; ☐ Placebo; ☒ Active.

	0 hr		Score			1/4 hr					1/2 hr				
	0	No	2	→	⇒	0	1	2	3	4	0	1	2	3	4
4		0		4	0										
3		21		3	63										
2		78		2	156								8	3	
1		1		1	1			4	4				33	10	
0		0		0	0		1	73	17			1	34	7	
-1		100		SUM	220			1					3	1	
-2															
-3															
-4															
	Initial Mean Score = 2.20					%Better = 8 %NC = 91 %W = 1 MS = (8-1)/100 0.07					%B = 54 %NC = 42 %W = 4 MS = (22+43-4)/100 0.61				

	1 hr					2 hr					4 hr				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4															
3			1					4	2					1	
2			29	10				27	9				5	1	
1		1	42	8			1	39	7				50	9	
0			4	3				7	3			1	22	8	
-1			2					1					1	2	
-2															
-3															
-4															
	%B = 91 %NC = 7 %W = 2 MS = (3+78+51-2)/100 1.30					%B = 89 %NC = 10 %W = 1 MS = (18+72+46-1)/100 1.35					%B = 64 %NC = 31 %W = 3 MS = (3+12+59-3)/100 0.71				

	4.5 hr					5.5 hr					8 hr				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4								1							
3			3	3				4	1						
2			27	7				27	10				11	6	
1			35	10				40	9				47	9	
0		1	13	1			1	6	1			1	20	6	
-1															
-2															
-3															
-4															
	%B = 85 %NC = 15 %W = 0 MS = (18+68+45)/100 1.31					%B = 92 %NC = 8 %W = 0 MS = (4+15+74+49)/100 1.42					%B = 73 %NC = 27 %W = 0 MS = (34+56)/100 0.90				

	8.5 hr					12 hr					12.5 hr				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4															
3			3	2				1	2				2		
2			23	8				19	3				29	8	
1		1	42	7				37	11			1	40	10	
0			10	3			1	20	4				7	3	
-1				1				1	1						
-2															
-3															
-4															
	%B = 86 %NC = 13 %W = 1 MS = (18+62+50-1)/100 1.29					%B = 73 %NC = 25 %W = 2 MS = (9+44+48-2)/100 0.99					%B = 90 %NC = 10 %W = 0 MS = (6+74+51)/100 1.31				

BEI 1025b

Table 5. Summation of data from Table 4 BEI 1025a and Table 4 BEI 1025b giving subjective evaluation made by 200 patients (100 active, 100 placebo) of their relief from the symptoms of stuffy nose, runny nose, sneezing, coughing, and muscle ache following the oral administration of phenylephrine HCl tablets (5 mg) or placebo tablets.

Which symptom is recoded below (Circle one); Stuffy Nose, Runny Nose, Sneezing, (Itching (Eyes, Nose)), Coughing, Muscle Ache

Data pertains to (Ck appropriate squares): ☐ Group 1; ☒ Group 2; ☐ Placebo; ☒ Active.

	0 hr			Score		1/4 hr					1/2 hr					1 hr					2 hr					4 hr				
	0	No	2		4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
50		0			4	0																								
49		0			3	0																								
48		0			2	0																								
47		3			1	3																								
46		97			0																									
45		100																												
44																														
43																														
42																														

Initial Mean Score = 0.03

	4.5 hr					5.5 hr					8 hr					8.5 hr					12 hr					12.5 hr				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
50																														
49																														
48																														
47																														
46																														
45																														
44																														
43																														
42																														

BEE 1025b

Table 9. Summation of data from Table 4 BEE 1025a and Table 4 BEE 1025b giving subjective evaluation made by 200 patients (100 active, 100 placebo) of their relief from the symptoms of stuffy nose, runny nose, sneezing, coughing, and muscle ache following the oral administration of phenylephrine HCl tablets (5 mg) or placebo tablets.

Which symptom is recoded below (Circle one); Stuffy Nose, Runny Nose, (Sneezing) Itching (Eyes, Nose), Coughing, Muscle Ache

Data pertains to (Ck appropriate squares): ☐ Group 1; ☒ Group 2; ☐ Placebo; ☒ Active.

0 hr

	0	No	2	Score	
4		0		4	0
3		5		3	15
2		67		2	134
1		28		1	28
0		0		0	0
		100	SUM	—	177

INITIAL MEAN SCORE = 1.77

1/4 hr

	0	1	2	3	4
4			1		
3					
2					
1			8	1	
0		25	41	3	
		3	17	1	

%B = 10
%NC = 69
%W = 21
MS = (4+9-21)/100 = -0.08

1/2 hr

	0	1	2	3	4
4			2		
3			5		
2		6	20	1	
1		14	28	2	
0		5	6		
		3	6	2	

%B = 78
%NC = 11
%W = 11
MS = (8+15+54+44-11)/100 = 1.10

1 hr

	0	1	2	3	4
4		1	2		
3		7	3		
2	5	21	7	1	
1	11	24	6		
0	3	5	1		
		2	1		

%B = 88
%NC = 9
%W = 3
MS = (12+30+68+41-3)/100 = 1.48

2 hr

	0	1	2	3	4
4		1	3		
3		4	11		
2		7	23	1	
1		14	22	3	
0		1	7	1	
		1	1		

%B = 89
%NC = 9
%W = 2
MS = (16+45+62+39-2)/100 = 1.60

4 hr

	0	1	2	3	4
4					
3			2		
2		3	13		
1		17	29	3	
0		7	18	1	
		2	4	1	

%B = 97
%NC = 2
%W = 1
MS = (6+32+49-7)/100 = 0.80

4.5 hr

	0	1	2	3	4
4			2		
3		4	7	1	
2		8	24	2	
1		10	24	2	
0		2	9		
		4	1		

%B = 84
%NC = 11
%W = 5
MS = (8+36+68+36-5)/100 = 1.43

5.5 hr

	0	1	2	3	4
4		1	3		
3		2	12	1	
2		7	21	3	
1		17	23	1	
0		1	7		
			1		

%B = 91
%NC = 8
%W = 1
MS = (16+45+62+41-1)/100 = 1.63

8 hr

	0	1	2	3	4
4			2		
3		2	5		
2		2	16		
1		15	26	2	
0		6	13	3	
		3	5		

%B = 70
%NC = 23
%W = 8
MS = (8+21+36+43-8)/100 = 1.00

8.5 hr

	0	1	2	3	4
4			3		
3		5	8		
2		5	20		
1		12	31	3	
0		3	4	2	
		3	1		

%B = 87
%NC = 9
%W = 4
MS = (12+39+50+46-4)/100 = 1.43

12 hr

	0	1	2	3	4
4			1		
3		2	10		
2		3	17		
1		12	24	4	
0		6	7	1	
		5	8		

%B = 73
%NC = 14
%W = 13
MS = (4+36+40+40-13)/100 = 1.07

12.5 hr

	0	1	2	3	4
4			5		
3		2	11	1	
2		13	17	2	
1		10	30	1	
0		3	3	1	
			1		

%B = 93
%NC = 6
%W = 1
MS = (20+42+64+41-1)/100 = 1.66

Table 9 [redacted] mination of data from Table 4 BEI 1025a and [redacted]le 4 BEI 1025b giving subjective evaluation mad[redacted] by 200 patients (100 active, 100 placebo) of their relief from the symptoms of stuffy nose, runny nose, sneezing, coughing, and muscle ache following the oral administration of phenylephrine HCl tablets (5 mg) or placebo tablets.

Which symptom is recoded below (Circle one); Stuffy Nose, Runny Nose, Sneezing, Itching (Eyes, Nose), (Coughing) Muscle Ache

Data pertains to (Ck appropriate squares): ☐ Group 1; ☒ Group 2; ☐ Placebo; ☒ Active.

	0 hr					1/4 hr					1/2 hr					1 hr					2 hr					4 hr				
	0	N_0	2	—	+	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4		0		4	0												1					1						1			
3		3		3	9																									
2		44		2	88																									
1		53		1	53		2	1				6	8	1			3	2				2	2				1			
0		0		0	0		42	41	3			39	33				17	16	2			15	18	1			9	10	1	
-1		100			150		9	2				8	3	2			31	26				35	23	1			39	34	2	
-2																	1		1				1	1			3			
-3																														
-4																														

Initial Mean Score = 1.50

%Better = 3
%NC = 43
%W = 11
MS = (3−11)/100 = −0.08

%B = 15
%NC = 73
%W = 13
MS = (15−13)/100 = 0.02

%B = 41
%NC = 57
%W = 2
MS = (41+10+35−2)/100 = 0.47

%B = 39
%NC = 59
%W = 2
MS = (39+4+34−2)/100 = 0.40

%B = 22
%NC = 75
%W = 3
MS = (22+2+20−3)/200 = 0.23

	4.5 hr					5.5 hr					8 hr					8.5 hr					12 hr					12.5 hr				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4		1					1					1					1					1						1			
3													1																		
2		4	4	2			6	6	1					1			1	2	1			2	1					1			
1		10	14				16	13	1			14	17	1			17	18	1			11	12	2			15	13	2		
0		33	25	1			29	25	1			34	26				34	24				39	31	1			37	30	1		
-1			1				1					4		1					1												
-2																														
-3																														
-4																														

%B = 35
%NC = 59
%W = 1
MS = (4+20+24−1)/100 = 0.47

%B = 44
%NC = 55
%W = 1
MS = (4+26+30−1)/100 = 0.32

%B = 35
%NC = 58
%W = 5
MS = (4+3+2+32−5)/100 = 0.36

%B = 41
%NC = 59
%W = 1
MS = (4+8+36−1)/100 = 0.47

%B = 39
%NC = 61
%W = 0
MS = (4+6+25)/100 = 0.35

%B = 37
%NC = 68
%W = 1
MS = (4+2+30)/100 = 0.36

1025b

9. Summation of data from Table 4 BEI 1025a and Table 4 BEI 1025b giving subjective evaluation made by 200 patients (100 active, 100 placebo) of their relief from the symptoms of stuffy nose, runny nose, sneezing, coughing, and muscle ache following the oral administration of phenylephrine HCl tablets (5 mg) or placebo tablets.

Which symptom is recorded below (Circle one); Stuffy Nose, Runny Nose, Sneezing, Itching (Eyes, Nose), (Coughing), Muscle Ache

Data pertains to (Ck appropriate squares): [X] Group 1; [ ] Group 2; [X] Placebo; [ ] Active.

	0 hr: No.	Score	No. × Score
4	0	4	0
3	4	3	12
2	40	2	80
1	52	1	52
0	4	0	0
-1	100	Sum	144
-2			
-3			
-4			

Initial Mean Score = 1.44

	1/4 hr 0	1	2	3	4	1/2 hr 0	1	2	3	4
4										
3										
2										
1		1				1	6	6	2	
0	4	47	38	4		3	37	32	2	
-1		4	2				9	2		
-2										
-3										
-4										

	1 hr 0	1	2	3	4	2 hr 0	1	2	3	4	4 hr 0	1	2	3	4
4															
3															
2			1												
1	1	7	7	2			12	10	2			7	8		
0	3	43	29	2		4	35	30	2		3	41	33	4	
-1		2	3				4	1			1	3			
-2															
-3															
-4															

1/4 hr: %Better = 15; %No Change = 79; %Worse = 6; Mean Score = (1-6)/100; 0.06

1/2 hr: %B = 15; %NC = 74; %W = 11; MS = (15-11)/100; 0.04

1 hr: %B = 18; %NC = 77; %W = 5; MS = (2+17-5)/100; 0.14

2 hr: %B = 24; %NC = 71; %W = 5; MS = (24-5)/100; 0.19

4 hr: %B = 15; %NC = 81; %W = 4; MS = (15-4)/100; 0.11

	4.5 hr 0	1	2	3	4	5.5 hr 0	1	2	3	4	8 hr 0	1	2	3	4
4															
3															
2		2	1				1	2					1		
1		6	12	2			13	16				8	11		
0	4	42	21	2		3	37	21	4		4	40	29	4	
-1		2	3			1	1	1				3			
-2															
-3															
-4															

	8.5 hr 0	1	2	3	4	12 hr 0	1	2	3	4	12.5 hr 0	1	2	3	4
4															
3															
2			1					1					1		
1		17	11	1			8	10				11	10	1	
0	4	35	27	3		4	42	29	4		4	41	25	3	
-1			1				2						4		
-2															
-3															
-4															

4.5 hr: %B 23; %NC 72; %W 5; MS = (6+20-5)/100; 0.21

5.5 hr: %B 32; %NC 65; %W 3; MS = (6+29-3)/100; 0.32

8 hr: %B 20; %NC 77; %W 3; MS = (2+19-3)/100; 0.18

8.5 hr: %B 30; %NC 69; %W 1; MS = (2+29-1)/100; 0.30

12 hr: %B 19; %NC 79; %W 2; MS = (2+18-2)/100; 0.18

12.5 hr: %B 23; %NC 73; %W 4; MS = (2+22-4)/100; 0.20

9. Examination of data from Table 4 BEF 1025a and Table 4 BEF 1025b giving subjective evaluation made by 200 patients (100 active, 100 placebo) of their relief from the symptoms of stuffy nose, runny nose, sneezing, coughing, and muscle ache following the oral administration of phenylephrine HCl tablets (5 mg) or placebo tablets.

Which symptom is recoded below (Circle one); Stuffy Nose, Runny Nose, Sneezing, Itching (Eyes, Nose), Coughing, (Muscle Ache)

Data pertains to (Ck appropriate squares): ☐ Group 1; ☒ Group 2; ☐ Placebo; ☒ Active.

	0 hr					1/4 hr					1/2 hr					1 hr					2 hr					4 hr				
	0	No.		Score	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4		0		4	0																									
3		1		3	3																									
2		31		2	62																									
1		59		1	59		2						5				6	8				8	9				6	8		
0		0		0	0	9	56	25	1		9	56	24	1		9	52	23	1		9	48	22	1		9	51	22	1	
		100			124		3	4				3	2				1					3					2	1		
Initial Score = 1.24						%B = 2 %NC = 91 %W = 7 MS = (2-7)/100 -0.05					%B = 5 %NC = 90 %W = 5 MS = (5-5)/100 0.0					%B = 14 %NC = 85 %W = 1 MS = (14-1)/100 0.13					%B = 17 %NC = 80 %W = 3 MS = (17-3)/100 0.14					%B = 14 %NC = 83 %W = 3 MS = (14-3)/100 0.11				

	4.5 hr					5.5 hr					8 hr					8.5 hr					12 hr					12.5 hr				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
4																														
3																														
2		1	1				1	2														4	4	3			10	9		
1		5	6				13	7				12	9				12	9												
0	9	53	24	1		9	43	21	1		9	44	22	1		9	46	22	1		7	41	20	12	9	9	49	22	1	
							2	1				3					1													
%B = 13 %NC = 87 %W = 0 MS = (4+11)/100 0.15						%B = 23 %NC = 74 %W = 3 MS = (6+20-3)/100 0.23					%B = 21 %NC = 76 %W = 3 MS = (21-3)/100 0.18					%B = 21 %NC = 78 %W = 1 MS = (21-1)/100 0.20					%B = 11 %NC = 89 %W = 0 MS = (11)/100 0.11					%B = 19 %NC = 81 %W = 0 MS = 19/100 0.19				

REFERENCE 11

Cohen, B. M., “Clinical and Physiologic Significance of Drug-Induced Changes in Nasal Flow/Resistance,” *European Journal of Clinical Pharmacology* 5:81-86, 1972.

Wyeth Study AHR-G1-A (EMC140 in Docket No. 1976N-0052N)

(Copy is in the review section of the background package.)

Wyeth Study 4010-3 (EMC140 in Docket No. 1976N-0052N)

(Copy is in the review section of the background package.)

Wyeth Study 7032 (EMC140 in Docket No. 1976N-0052N)

(Copy is in the review section of the background package.)

REFERENCE 15

INTER-OFFICE MEMORANDUM
STERLING-WINTHROP RESEARCH INSTITUTE
RENSSELAER, NEW YORK

June

To: Dr. Suter

From: N. A. Hulme

Re: Nasal Decongestant Study by Elizabeth Biochemical

A study was conducted at the Elizabeth Biochemica
under the technical direction of Mr. John Boffa and me
Dr. George Rucker for the purpose of evaluating a modi
flow device as a clinically useful instrument for meas
nasal patency. The apparatus itself was built at Ster
was patterned after a similar device of the Vick's Com
Elizabeth Biochemical Laboratories has had considerable

Methods

The study was conducted in two phases. The first
compare the Sterling-Winthrop instrument to a Vick's Co
the purpose of calibrating and determining relative sen
resistance changes. Included in this phase was a direc
two instruments in three subjects representing a known
nasal resistances. The second phase was designed to ev
as an instrument for measuring changes in air resistanc
subjects having demonstrable nasal congestion.

The latter phase of the study consisted of actuall
air resistances in 25 subjects having head colds. The
medicated on a double blind crossover basis with ephedr
a known orally active decongestant, a placebo, and 25 m
The latter was included in the study for the purpose of
possible lead for subsequent studies on the effectivenes
administered Neo-Synephrine. The dose used was one show
study (Stander 1-5-67) in Institute volunteers to have n
pressure and only a minor effect on pulse rate.

All subjects reported for two consecutive days for
measurements. Medication was given in a randomized code
pairs of either placebo and ephedrine, or placebo and Ne
each subject always received placebo

Actual measurements were carried out by taking five nasal air resistance readings for each nostril at 0, 15 and 30 minute periods before medication and at 15, 30, 45, 60 and 120 minute intervals following medication. The five readings obtained from each nostril were combined and the means used for calculation purposes.

At the time of each control and postmedication air resistance measurement each subject was asked to describe his congestion. This was recorded as being closest to one of the following statements and was then scored as indicated.

Degree of Congestion	Score
Nose feels clear	0
Almost clear	1
Stuffy	2
Very stuffy	3
Completely blocked	4

The appearance of each subject's turbinates was observed at the 0 and 30 minute time intervals before medication and again 60 and 120 minutes following medication. The observer recorded appearance as being normal, inflamed, or gray and badly swollen.

Results

The results of the first phase demonstrated equivalence of the Institute instrument to the Vick's device in terms of sensitivity to air resistance changes as well as functional usefulness. Additionally, the apparatus when cross-checked against the Vick's machine in three volunteers having different states of congestion resulted in equivalent readings (Table I).

The results of the air resistance section of the study were analyzed by Mr. Stander in terms of differences observed between placebo and either of the two active medications. The actual changes in air resistance values from zero time are given in Table II. These data are plotted as graphs for the placebo:ephedrine subjects and placebo:Neo-Synephrine subjects in Figures 1 and 2 respectively. The two sets of curves are remarkably similar and appear to be essentially superimposable except for a slight shift to the right for the Neo-Synephrine curve in Figure 1, possibly indicating a minor delay in absorption time. The mean values for each subject at the indicated time intervals are provided in the Appendix.

The sccres recorded for the degree of congestion felt by the subjects were also analyzed by Mr. Stander and comparisons were made as the sum of the differences between placebo and active medication for each

of the subjects. These differences and the statistical significance between treatments for the placebo:Neo-Synephrine pair are given in Table III and those for the placebo:ephedrine pair in Table IV. These data indicate a positive correlation between the objective measurements as defined by the air resistance readings and the subjective impression of the patient in terms of relief of congestion. This correlation is of particular interest inasmuch as Elizabeth Biochemical Laboratories had reported they had not observed this in previous studies.

Observations on turbinate appearance did not produce any trends that could be interpreted in terms of medication response.

Conclusions

It is quite apparent from the results that Neo-Synephrine when administered in a 25 mg oral dose is an effective decongestant and is comparable in effect to ephedrine at an 8 mg dose. Whether this is a minimum effect or perhaps even a maximum response is difficult to determine without carrying out additional studies of a dose ranging type. It is suggested that this would be the next logical step, that is, to do a study on the comparative decongestant effects at several Neo-Synephrine dose levels.

The primary purpose of the study, that is, to evaluate the Institute air flow instrument has been accomplished so that we now have an instrument capable of application in a fairly broad range of decongestant studies. Inasmuch as experience with the instrument is limited to the one laboratory it would be advisable to have at least one additional group develop proficiency to increase the over-all source of clinical material available. Also, it would be advisable in some future program to include another method for measuring decongestion such as that of Connell (Roosevelt Hospital, New York) using Electronic Nasography or McLaurin's (Tulane) method of anterior rhinometry.

N. A. Hulme

bjc

cc: Dr. Wessinger
JGB > WPB > TEL > CL > DM
Dr. Lands
Mr. Stander
Dr. Luduena
Dr. Surrey
Dr. Cox
File (4)

Table I

COMPARISON OF SWRI AND VICK'S NASAL AIR FLOW INSTRUMENTS
IN SUBJECTS HAVING DIFFERENT DEGREES OF CONGESTION

Subject	Time	Resistance Measurements*			
		SWRI		Vicks	
		L. Nostril	R. Nostril	L. Nostril	R. Nostril
RB	0	31.6	32.6	29.6	29.8
	10	32.8	33.8	30.6	30.2
	20	32.4	33.2	29.8	30.8
PE	0	17.6	18.4	15.2	17.8
	10	17.8	18.6	16.6	16.6
	20	18.2	18.4	18.8	17.6
JB	0	8.8	9.8	7.6	8.6
	10	9.4	10.2	7.8	8.8
	20	9.6	9.6	8.0	8.6

*Each value is the average of 5 separate readings

Table II

COMPARISON OF THE NASAL DECONGESTANT EFFECT OF ORAL EPHEDRINE (8mg) AND NEO-SYNEPHRINE (25mg) VERSUS PLACEBO IN SUBJECTS WITH "COMMON COLD"

Objective Measurements[A]

	t_0	$t_{15}-t_0$	$t_{30}-t_0$	$t_{45}-t_0$	$t_{60}-t_0$	$t_{90}-t_0$	$t_{120}-t_0$
Ephedrine (8 mg)	12.2	-0.79	-2.9	-4.6	-4.7	-4.2	-3.3
Placebo	12.1	0.14	0.49	0.36	0.64	0.64	0.62
Analysis of Variance Comparisons between treatments	p>0.05	p=0.01	p=0.01	p=0.01	p=0.01	p=0.01	p=0.01
Neo-Synephrine (25 mg)	12.8	-0.38	-2.8	-4.2	-5.2	-4.7	-4.0
Placebo	13.0	-0.0083	0.067	0.31	0.77	0.77	0.85
Analysis of Variance Comparisons between treatments	p>0.05	p>0.05	p=0.01	p=0.01	p=0.01	p=0.01	p=0.01

[A]Includes 13 Subjects for Ephedrine and 12 Subjects for Neo-Synephrine

Fig. I COMPARISON OF THE NASAL DECONGESTANT EFFECT OF ORAL NEO-SYNEPHRINE® (25mg) AND PLACEBO IN 12 SUBJECTS WITH "COMMON COLD"

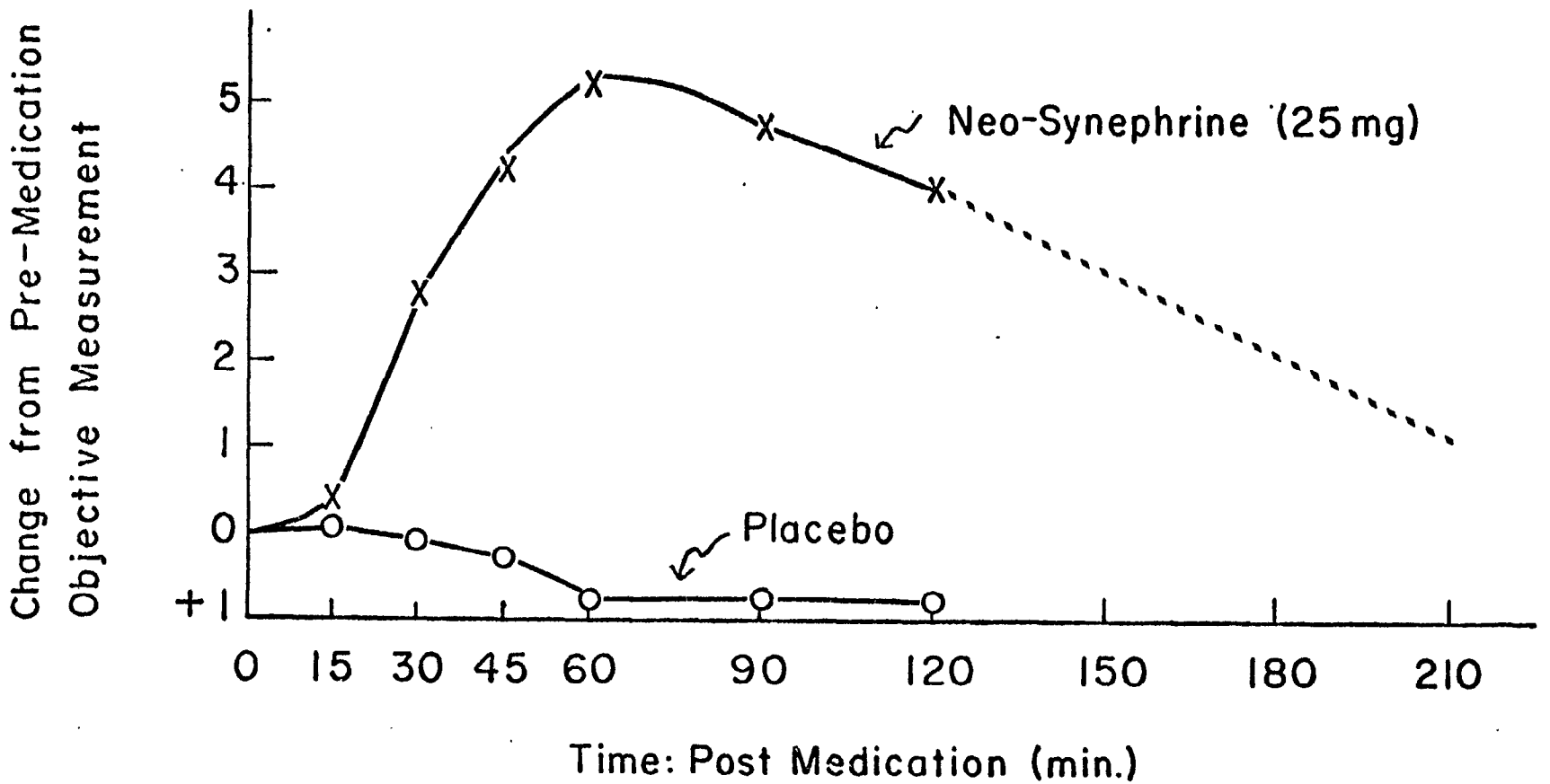


Fig. 2 COMPARISON OF THE NASAL DECONGESTANT EFFECT OF ORAL EPHEDRINE (8 mg) AND PLACEBO IN 13 SUBJECTS WITH "COMMON COLD"

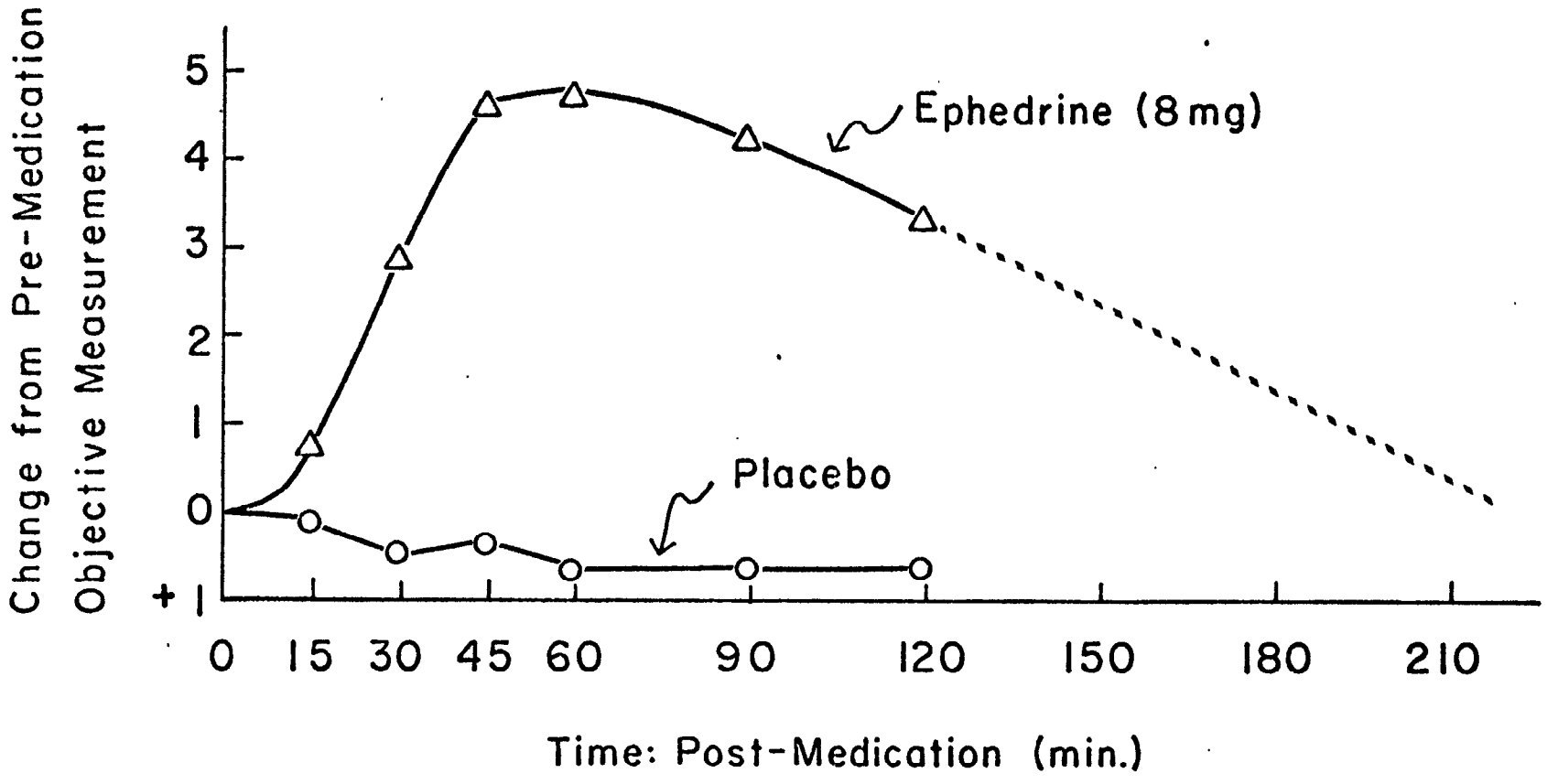


Table III

COMPARISON OF THE NASAL DECONGESTANT EFFECT
OF ORAL NEO-SYNEPHRINE (25 mg) AND PLACEBO
IN 12 SUBJECTS WITH "COMMON COLD"

Sum of the Subjective Impression Differences

Patient	Neo-Synephrine (25 mg)	Placebo
002	-10	+3
004	0	-7
006	-5	+2
007	+1	0
009	-5	0
012	-6	-3
014	-1	+2
015	-6	0
017	-5	0
019	-6	-2
021	-3	+3
023	-6	-2
Median	-5	0

Significance of the difference between treatments; p=0.01
Wilcoxon Matched-Pairs Signed-Ranks test

Table IV

COMPARISON OF THE NASAL DECONGESTANT EFFECT
OF ORAL EPHEDRINE (8 mg) AND PLACEBO
IN 13 SUBJECTS WITH "COMMON COLD"

Sum of the Subjective Impression Differences

Patient	Ephedrine (8 mg)	Placebo
001	-11	+3
003	0	-5
005	-5	-5
008	0	0
010	-11	-5
011	-6	-1
013	-7	0
016	-4	0
018	-9	-2
020	-5	-1
022	-7	-2
024	-7	-6
025	-8	-2
Median	-7	-2

Significance of the difference between treatments; p=0.01
Wilcoxon Matched-Pairs Signed-Ranks test

APPENDIX

Objective Measurement Means*

Patient	Treatment	t_0	t_{15}	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}
002	Neo-Synephrine	9.0	9.0	7.5	5.5	5.5	5.5	6.4
	Placebo	9.7	9.6	9.8	10.7	10.5	11.2	11.3
004	Neo-Synephrine	11.6	11.5	7.5	6.4	4.9	5.9	7.6
	Placebo	12.4	12.3	12.8	12.6	13.7	13.5	12.5
006	Neo-Synephrine	11.7	11.2	6.5	6.0	6.6	6.5	7.5
	Placebo	13.4	12.5	12.7	13.0	13.6	13.3	13.3
007	Neo-Synephrine	18.3	17.6	15.9	14.5	11.5	13.0	16.0
	Placebo	13.5	13.6	13.7	13.5	14.5	14.5	14.5
009	Neo-Synephrine	15.5	15.4	11.4	9.3	7.6	7.5	8.5
	Placebo	13.3	13.5	13.5	14.0	13.9	14.4	14.5
012	Neo-Synephrine	13.8	13.1	10.9	10.6	7.9	8.2	7.8
	Placebo	15.8	16.4	16.5	16.5	17.3	17.5	16.8
014	Neo-Synephrine	11.7	11.3	10.4	7.9	6.9	7.9	7.3
	Placebo	15.5	15.5	15.5	16.5	17.0	15.5	17.0
015	Neo-Synephrine	15.9	14.6	11.3	10.5	11.0	9.9	10.4
	Placebo	11.3	11.6	11.7	12.0	12.3	12.3	12.6
017	Neo-Synephrine	11.5	11.0	10.5	8.7	7.0	7.5	6.7
	Placebo	9.6	10.0	9.0	9.4	10.1	10.6	11.5
019	Neo-Synephrine	11.5	11.3	10.5	8.4	7.3	8.3	8.9
	Placebo	11.6	11.7	12.0	11.9	12.2	11.9	11.7
021	Neo-Synephrine	13.0	12.7	10.1	7.5	8.3	10.0	10.0
	Placebo	19.0	18.4	18.7	18.0	18.0	18.5	18.6
023	Neo-Synephrine	10.1	10.4	7.9	8.1	6.4	7.0	8.8
	Placebo	10.7	10.6	11.5	11.4	11.9	11.8	11.7

*Each number represents the mean of 5 measurements on both right and left nostrils.

APPENDIX

Objective Measurement Means*

Patient	Treatment	t_0	t_{15}	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}
001	Ephedrine	9.7	9.5	6.9	6.0	6.5	6.4	6.8
	Placebo	9.7	9.9	9.8	10.2	11.0	11.3	11.4
003	Ephedrine	11.3	11.5	8.5	7.3	6.9	6.6	8.0
	Placebo	10.4	10.4	10.6	10.8	10.6	10.7	10.7
005	Ephedrine	12.5	11.7	11.0	7.5	6.5	8.5	11.5
	Placebo	11.5	11.4	12.4	11.5	11.7	11.9	12.3
008	Ephedrine	15.4	15.4	12.9	11.4	11.1	11.3	14.0
	Placebo	16.5	15.7	15.6	16.4	16.8	17.2	17.0
010	Ephedrine	12.5	11.5	8.8	7.5	7.9	7.5	9.3
	Placebo	12.0	11.7	11.6	9.1	8.5	9.0	9.9
011	Ephedrine	11.2	10.2	7.9	6.5	8.5	8.8	8.5
	Placebo	11.6	11.4	11.6	12.1	12.5	12.6	12.4
013	Ephedrine	13.6	13.6	10.0	8.6	7.5	8.5	7.3
	Placebo	11.4	11.5	11.5	11.9	12.6	12.0	11.9
016	Ephedrine	12.6	12.0	9.1	7.9	7.0	8.4	8.9
	Placebo	13.3	13.4	13.8	13.9	14.5	14.4	14.5
018	Ephedrine	12.5	11.9	10.3	6.9	6.9	8.5	8.7
	Placebo	14.3	15.1	15.4	15.5	16.7	17.5	16.5
020	Ephedrine	12.3	11.1	10.5	6.0	6.0	6.3	6.5
	Placebo	12.7	13.0	13.0	13.5	13.4	13.5	13.5
022	Ephedrine	12.3	10.6	7.6	8.0	8.7	9.5	10.4
	Placebo	11.5	12.2	12.7	12.9	13.5	12.0	12.6
024	Ephedrine	10.5	9.5	7.5	7.9	6.6	6.4	6.5
	Placebo	11.7	12.0	12.5	12.9	12.5	12.4	12.4
025	Ephedrine	12.0	10.0	9.6	7.7	7.0	7.5	8.9
	Placebo	10.9	11.6	11.6	11.5	11.5	11.3	10.5

*Each number represents the mean of 5 measurements on both right and left nostrils.

REFERENCE 16

INTER-OFFICE MEMORANDUM

STERLING-WINTHROP RESEARCH INSTITUTE

RENSSELAER, NEW YORK

OK R&D Ref #6

June 2, 1969

Ref #8

To: Dr. Blackmore

From: N. A. Hulme

Re: Oral Neo-Synephrine - Elizabeth Biochemical Study No. 3

Following the decision made in February 1968 to expand the oral decongestant studies a protocol was proposed and approved (March 6, 1968) in which Elizabeth Biochemical Labs was to evaluate Neo-Synephrine at doses of 5, 15 and 25 mg and phenylpropanolamine at a dose of 50 mg. The latter medication was added to provide comparative data on a known orally active decongestant at its highest accepted dose. The various Neo-Synephrine dosages were chosen to provide data on low, intermediate and upper levels. In order to provide comparative information on side effects, pulse and blood pressure readings were obtained at periodic intervals in addition to the objective airflow readings and subjective impressions of improvement.

The details of the study along with the statistical analysis of the results, provided by Mr. Stander, are presented below.

Protocol and Methodology

A total of 46 subjects with head colds and having confirmed nasal congestion on two consecutive days participated in the study. Evaluation of the degree of nasal congestion was made by measuring the relative resistance to a constant flow of air passing through the nasal passageway by a modification of the Butler-Ivy procedure (Blanchard et al E.E.N.T. Monthly 43, 76-82, 1964).

The subjects were assigned coded drugs on a double-blind randomized basis. The randomization was designed so that half the subjects in each dose category received placebo on the first day and active medication on the second day. The reversed sequence occurred with the other subjects. The following table gives the number of subjects receiving each of the drugs.

No. of Subjects	Neo-Synephrine vs. Placebo	Phenylpropanolamine vs. Placebo
16	5 mg	-
10	15 mg	-
10	25 mg	-
10	-	50 mg

3.6
16 - 5

All drugs were supplied in identical capsules and packaged in individual preassigned envelopes labeled by code number and subject number.

Objective measurements of airflow resistance were carried out by obtaining five consecutive readings for each nostril at 0, 15 and 30 minutes before medication and 15, 30, 45, 60, 120 and 240 minute intervals following medication. The ten readings from both nostrils were combined and the arithmetic means employed for further calculations and analysis.

Subjective impressions of changes in nasal congestion were obtained by having each subject describe his congestion at the time each set of airflow measurements were made. These were classified as being closest to one of the following conditions:

Degree of Congestion
Nose feels clear
Almost clear
Stuffy
Very stuffy
Completely blocked

A shift of one degree of congestion from the premedication state was graded as plus or minus 1, a shift in two degrees as plus or minus 2, etc. The sums of the change at each time interval were recorded for each subject. The median change for all subjects on each active medication dosage was compared to the same subject's placebo scores for significance of the difference.

Pulse and sitting blood pressure readings were obtained on each subject at 30, 15 and 0 minutes before medication and at 30, 60, 90, 120, 180 and 240 minutes following medication. The readings from each medication group were combined and the arithmetic means employed for further calculations and analysis. This provided comparisons between active medication and placebo for diastolic pressure, systolic pressure and pulse rate.

Results

The mean of the air resistance readings for each subject was analyzed for significance between the placebo and medication groups at each of the time intervals (see Appendix). The levels of significance for each of the drugs at the indicated time interval are given in Table 1. The means were also calculated as the percent (fractional units x 100) change from the last premedication reading. These data with the levels of significance are given in Table II. The data plotted as graphs for each medication:placebo pair are given in Figures 1 to 4.

The objective readings show significant differences occuring between placebo and all three doses of Neo-Synephrine in addition to the 50 mg dose of phenylpropanolamine. These differences occurred as early as the 15 minute postmedication reading with the 15 mg dose of Neo-Synephrine

and with phenylpropanolamine and was apparent at the 30 minute reading with the other two Neo-Synephrine medications. Significant differences continued to occur four hours after medication with all but the 25 mg level of Neo-Synephrine.

A comparison was made of the sum of the subjective difference changes in the degree of congestion reported for each of the medications. These differences with the levels of statistical significance between treatments for the drug:placebo pair are given in Table III. As will be noted a statistically significant difference, correlating with drug therapy occurred in subjects receiving 15 mg Neo-Synephrine and 50 mg phenylpropanolamine. The differences occurring with the 5 and 25 mg doses were not statistically different although the numerical difference at the 25 mg dose was considerable.

Analysis of the pulse rate data indicated that periods of statistically significant differences occurred between placebo and Neo-Synephrine 5 mg and 25 mg, but not at the 15 mg dose or with phenylpropanolamine (see Table IV). The greatest difference was of the order of 4 beats per minute and is not considered to be of clinical importance.

Analysis of the systolic blood pressure data showed statistically significant differences at the 120 minute reading at the 5 and 15 mg Neo-Synephrine dose but not at the 25 mg dose. Patients receiving 50 mg phenylpropanolamine had statistically significant changes in systolic pressure at the 30, 60, 90, and 120 minute time periods. These changes were equivalent to a somewhat less than 2 mm increase with the Neo-Synephrine and are not of clinical significance. The changes on phenylpropanolamine reached a maximum of 9 mm increase at the 60 minute time period and are of questionable clinical importance (see Table V).

The diastolic pressure was analyzed and showed statistically significant differences at the 90 minute reading on the 5 mg Neo-Synephrine dose, at the 120 minute reading on the 15 mg dose and no significant changes on 25 mg. Phenylpropanolamine produced significant increases at the 60 and 90 minute readings. The latter were of the order of a maximum 6 mm increase and about a 3 mm increase on Neo-Synephrine. These changes are not considered to be of clinical importance (see Table VI).

Discussion

Several points of interest have resulted from this study. One is the rather unexpected finding that 5 mg of Neo-Synephrine produced objective changes in nasal resistance; although, at this dose the comparable subjective readings did not show a similar picture Data from 16 subjects were available for analysis at this dose as against 8 or 9 for the other medications. This tended to increase the sensitivity of the assay procedure for this particular dosage.

Another pattern which seems to be emerging is the lack of a strong dose response relationship with Neo-Synephrine. In this study the objective changes produced by the 5, 15 and 25 mg doses were nearly the same. This was true also of the Cintest study (Hulme to Blackmore 4-10-69) in which the 25 mg dose produced approximately the same picture as the 10 mg dose. Similarly in the earlier Elizabeth study (Hulme to Wessinger 1-12-68) the 10 and 15 mg doses produced essentially the same results; although, in this particular study the 25 mg dose did appear to be more effective than the lower levels.

Phenylpropanolamine at 50 mg may turn out to be somewhat more effective than Neo-Synephrine. In this study the magnitude of the air resistance change was greater than with any of the Neo-Synephrine doses; although, this did not appear to be true in the Cintest study. In the Huntingdon study (Hulme to Blackmore 5-13-69) phenylpropanolamine produced significant air resistance changes; whereas, Neo-Synephrine at 10 and 25 mg did not.

The ability to correlate subjective feelings of improvement with objective results is analyzed as an all or none response, that is, a correlation either does or does not occur at each particular dose. In this study a positive correlation was found at the 15 mg dose of Neo-Synephrine and the 50 mg dose of phenylpropanolamine but not at the 5 or 25 mg level of Neo-Synephrine. In previous studies a positive correlation was found with 10 mg Neo-Synephrine and with phenylpropanolamine but not with 25 mg Neo-Synephrine by the Cintest group. The earlier Elizabeth study resulted in a positive correlation at 10 mg, 15 mg of Neo-Synephrine and 50 mg ephedrine but not at 25 mg Neo-Synephrine; yet the first Elizabeth study (Hulme to Suter 6-27-67) showed a positive correlation between 25 mg Neo-Synephrine and subjective relief. It would therefore appear that the ability to detect subjective changes may be at or near a threshold level due possibly either to the technique of evaluation or possibly to a borderline drug effect.

The pulse and blood pressure changes observed at the 5, 15 and 25 mg doses of Neo-Synephrine and described above under Results were minimal and of no clinical significance.

No side effects were reported by any subject receiving the Neo-Synephrine capsules. One subject receiving 50 mg phenylpropanolamine reported an increased heart rate and a nauseous feeling about 20 minutes after taking the capsule.

N. A. Hulme

bjc
cc: Dr. Wessinger, Dr. Luduena, Mr. Stander, Dr. Cox, Dr. Surrey, Mr. Heike, Dr. Gerding, Dr. Rees, Dr. Giambalvo, File

Table I

COMPARISON OF THE NASAL DECONGESTANT EFFECT OF ORAL PHENYLPROPANOLAMINE (50 mg) AND NEO-SYNEPHRINE (5 mg, 15 mg, 25 mg) VERSUS PLACEBO IN SUBJECTS WITH "COMMON COLD"

Objective Measurements

	t_0	t_{15}/t_0	t_{30}/t_0	t_{45}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0	t_{180}/t_0	t_{240}/t_0
Neo-Synephrine (5 mg)	12.88	-0.14	-1.61	-3.11	-3.56	-3.22	-2.02	-1.61	-1.40
Placebo	11.99	0.11	0.41	0.71	0.49	0.84	0.82	0.83	0.22
Analysis of Variance (s) (n = 16)	p>0.05 (1.41)	p>0.05 (0.46)	p=0.01 (1.11)	p=0.01 (1.20)	p=0.01 (1.89)	p=0.01 (1.75)	p=0.01 (1.42)	p=0.01 (1.46)	p=0.05 (2.07)
Neo-Synephrine (15 mg)	13.72	-0.60	-1.16	-2.74	-3.22	-3.21	-2.86	-2.51	-3.08
Placebo	13.11	0.21	0.10	0.35	0.08	0.50	0.24	0.02	0.26
Analysis of Variance (s) (n = 8)	p>0.05 (0.80)	p=0.01 (0.31)	p=0.05 (0.98)	p=0.01 (1.66)	p=0.05 (2.06)	p=0.01 (1.54)	p=0.01 (1.45)	p=0.01 (1.44)	p=0.05 (2.31)
Neo-Synephrine (25 mg)	13.91	-0.10	-2.26	-3.61	-5.01	-4.04	-3.37	-2.52	-2.20
Placebo	13.79	-0.01	-0.58	-0.60	-0.84	-0.77	-0.43	0.01	-0.79
Analysis of Variance (s) (n = 9)	p>0.05 (1.70)	p>0.05 (0.88)	p>0.05 (3.03)	p>0.05 (3.55)	p>0.05 (3.98)	p>0.05 (3.53)	p>0.05 (3.06)	p>0.05 (3.51)	p>0.05 (2.52)
Phenylpropanolamine (50 mg)	13.10	-1.09	-4.33	-5.57	-6.38	-6.18	-5.22	-3.93	-3.59
Placebo	12.47	0.38	0.49	0.66	0.56	1.06	1.06	0.59	-0.19
Analysis of Variance (s) (n = 9)	p>0.05 (1.31)	p=0.01 (0.70)	p=0.01 (0.91)	p=0.01 (0.88)	p=0.01 (1.46)	p=0.01 (1.80)	p=0.01 (2.09)	p=0.01 (2.57)	p=0.05 (2.29)

Table II

COMPARISON OF THE NASAL DECONGESTANT EFFECT OF ORAL PHENYLPROPANOLAMINE (50 mg) AND NEO-SYNEPHRINE (5 mg, 15 mg, 25 mg) VERSUS PLACEBO IN SUBJECTS WITH "COMMON COLD"

Objective Measurements (fractional units x 100)

	t_0	t_{15}/t_0	t_{30}/t_0	t_{45}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0	t_{180}/t_0	t_{240}/t_0
Neo-Synephrine (5 mg)	12.88	0.99	0.88	0.76	0.73	0.76	0.85	0.88	0.99
Placebo	11.99	1.01	1.04	1.06	1.04	1.07	1.07	1.08	1.02
Analysis of Variance (n = 16)	p>0.05 (1.41)	p>0.05 (.047)*	p=0.01 (.123)	p=0.01 (.139)	p=0.01 (.178)	p=0.01 (.162)	p=0.01 (.147)	p=0.01 (.166)	p=0.05 (.164)
Neo-Synephrine (15 mg)	13.72	0.96	0.91	0.78	0.75	0.75	0.77	0.81	0.77
Placebo	13.11	1.02	1.01	1.03	1.01	1.04	1.02	1.00	1.01
Analysis of Variance (n = 8)	p>0.05 (0.80)	p=0.01 (.047)	p>0.05 (.123)	p=0.01 (.139)	p=0.01 (.178)	p=0.01 (.162)	p=0.01 (.147)	p=0.05 (.166)	p=0.01 (.164)
Neo-Synephrine (25 mg)	13.91	0.99	0.83	0.73	0.64	0.71	0.76	0.83	0.86
Placebo	13.79	0.99	0.96	0.96	0.95	0.95	0.98	1.00	0.94
Analysis of Variance (n = 9)	p>0.05 (1.70)	p>0.05 (.047)	p=0.05 (.123)	p=0.01 (.139)	p=0.01 (.178)	p=0.01 (.162)	p=0.01 (.147)	p=0.05 (.166)	p>0.05 (.164)
Phenylpropanolamine (50 mg)	13.10	0.92	0.66	0.56	0.52	0.54	0.61	0.71	0.75
Placebo	12.47	1.03	1.04	1.06	1.05	1.09	1.09	1.05	0.98
Analysis of Variance (n = 9)	p>0.05 (1.31)	p=0.01 (.047)	p=0.01 (.123)	p=0.01 (.139)	p=0.01 (.178)	p=0.01 (.162)	p=0.01 (.147)	p=0.01 (.166)	p=0.01 (.164)

*All postmedication values are pooled estimates of the standard deviation

Table II

COMPARISON OF THE NASAL DECONGESTANT EFFECT OF ORAL NEO-SYNEPHRINE (5 mg, 15 mg, 25 mg) AND PHENYLPROPANOLAMINE (50 mg) VERSUS PLACEBO IN SUBJECTS WITH "COMMON COLD"

Subjective Impression Differences

	Median Difference	Analysis of Variance	Standard Deviation	Number of Subjects
Neo-Synephrine 5 mg	-6.56	p>0.05	3.71	16
Placebo	-5.78			
Neo-Synephrine 15 mg	-5.87	p=0.05	4.10	8
Placebo	-2.25			
Neo-Synephrine 25 mg	-6.56	p>0.05	2.10	9
Placebo	-3.88			
Phenylpropanolamine 50 mg	-9.33	p=0.05	3.74	9
Placebo	-3.67			

Table IV

COMPARISON OF THE EFFECT OF ORAL NEO-SYNEPHRINE (5 mg, 15 mg, 25 mg) AND PHENYLPROPANOLAMINE (50 mg) ON THE PULSE RATE IN SUBJECTS WITH "COMMON COLD"

	t_0	t_{30}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0	t_{180}/t_0	t_{240}/t_0
Neo-Synephrine (5 mg)	71.12	1.01	1.02	1.04	1.03	1.01	1.01
Placebo	75.25	0.97	0.98	0.98	0.99	0.99	0.96
Analysis of Variance (s) (n = 16)	p>0.05 (6.60)	p=0.05 (.04)	p>0.05 (.06)	p=0.01 (.05)	p>0.05 (.06)	p>0.05 (.08)	p>0.05 (.10)
Neo-Synephrine (15 mg)	77.25	0.99	0.99	0.99	0.99	1.01	1.01
Placebo	74.00	1.00	0.99	1.01	0.98	1.03	1.03
Analysis of Variance (s) (n = 8)	p>0.05 (4.53)	p>0.05 (.06)	p>0.05 (.06)	p>0.05 (.04)	p>0.05 (.08)	p>0.05 (.04)	p>0.05 (.10)
Neo-Synephrine (25 mg)	80.89	1.02	1.00	1.01	0.99	1.00	0.96
Placebo	82.22	0.99	0.99	1.00	0.97	0.99	1.02
Analysis of Variance (s) (n = 9)	p>0.05 (6.28)	p=0.05 (.03)	p>0.05 (.04)	p>0.05 (.03)	p>0.05 (.02)	p>0.05 (.04)	p=0.05 (.04)
Phenylpropanolamine (50 mg)	79.33	1.05	1.05	1.03	1.02	1.00	0.99
Placebo	74.00	1.00	1.01	1.00	1.02	1.02	1.01
Analysis of Variance (s) (n = 9)	p>0.05 (7.58)	p>0.05 (.06)	p>0.05 (.06)	p>0.05 (.07)	p>0.05 (.08)	p>0.05 (.04)	p>0.05 (.06)

Tab

COMPARISON OF THE EFFECT OF ORAL NEO-SYNEPHRINE (5 mg, 15 mg, 25 mg) AND PHENYLPROPANOLAMINE (50 mg) ON THE SYSTOLIC BLOOD PRESSURE IN SUBJECTS WITH "COMMON COLD"

	t_0	t_{30}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0	t_{180}/t_0	t_{240}/t_0
Neo-Synephrine (5 mg)	125.19	1.00	1.00	1.01	1.01	1.00	1.00
Placebo	126.00	0.99	0.99	1.00	0.99	0.98	0.99
Analysis of Variance (s) (n = 16)	p>0.05 (3.58)	p>0.05 (.02)	p>0.05 (.02)	p>0.05 (.03)	p=0.05 (.02)	p>0.05 (.03)	p>0.05 (.04)
Neo-Synephrine (15 mg)	136.12	1.00	1.00	1.01	1.00	1.00	1.00
Placebo	136.75	1.00	0.99	1.00	0.98	1.00	1.00
Analysis of Variance (s) (n = 8)	p>0.05 (3.87)	p>0.05 (.02)	p>0.05 (.03)	p>0.05 (.02)	p=0.05 (.02)	p>0.05 (.01)	p>0.05 (.03)
Neo-Synephrine (25 mg)	125.89	1.01	1.01	1.01	1.00	1.00	0.99
Placebo	122.89	1.00	1.00	1.01	1.01	1.01	1.00
Analysis of Variance (s) (n = 9)	p>0.05 (3.87)	p>0.05 (.02)	p>0.05 (.02)	p>0.05 (.03)	p>0.05 (.02)	p>0.05 (.02)	p>0.05 (.02)
Phenylpropanolamine (50 mg)	136.67	1.05	1.07	1.06	1.04	1.03	1.01
Placebo	136.89	1.00	1.00	1.00	1.00	1.01	0.99
Analysis of Variance (s) (n = 9)	p>0.05 (5.73)	p=0.05 (.04)	p=0.01 (.05)	p=0.01 (.03)	p=0.05 (.03)	p>0.05 (.03)	p>0.05 (.02)

Table I

COMPARISON OF THE EFFECT OF ORAL NEO-SYNEPHRINE (5 mg, 15 mg, 25 mg) AND PHENYLPROPANOLAMINE (50 mg) ON THE DIASTOLIC BLOOD PRESSURE IN SUBJECTS WITH "COMMON COLD"

	t_0	t_{30}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0	t_{180}/t_0	t_{240}/t_0
Neo-Synephrine (5 mg)	76.25	1.00	1.02	1.03	1.01	0.99	1.02
Placebo	76.06	0.98	1.00	0.99	1.00	0.98	0.99
Analysis of Variance (s) (n = 16)	p>0.05 (3.76)	p>0.05 (.04)	p>0.05 (.04)	p=0.05 (.04)	p>0.05 (.05)	p>0.05 (.04)	p>0.05 (.05)
Neo-Synephrine (15 mg)	80.25	1.01	1.00	1.00	1.01	0.99	1.02
Placebo	81.25	1.00	0.98	0.99	0.98	1.00	1.01
Analysis of Variance (s) (n = 8)	p>0.05 (2.00)	p>0.05 (.02)	p>0.05 (.04)	p>0.05 (.03)	p=0.05 (.02)	p>0.05 (.03)	p>0.05 (.08)
Neo-Synephrine (25 mg)	78.89	1.01	1.03	1.04	1.02	1.00	0.99
Placebo	78.89	0.99	1.01	1.01	1.02	0.99	0.99
Analysis of Variance (s) (n = 9)	p>0.05 (3.67)	p>0.05 (.03)	p>0.05 (.05)	p>0.05 (.04)	p>0.05 (.04)	p>0.05 (.03)	p>0.05 (.05)
Phenylpropanolamine (50 mg)	79.89	1.05	1.05	1.03	1.03	1.02	1.00
Placebo	85.33	1.00	0.97	0.96	0.97	0.97	0.96
Analysis of Variance (s) (n = 9)	p=0.05 (4.57)	p>0.05 (.05)	p=0.05 (.06)	p=0.05 (.06)	p>0.05 (.06)	p>0.05 (.09)	p>0.05 (.08)

Figure 1

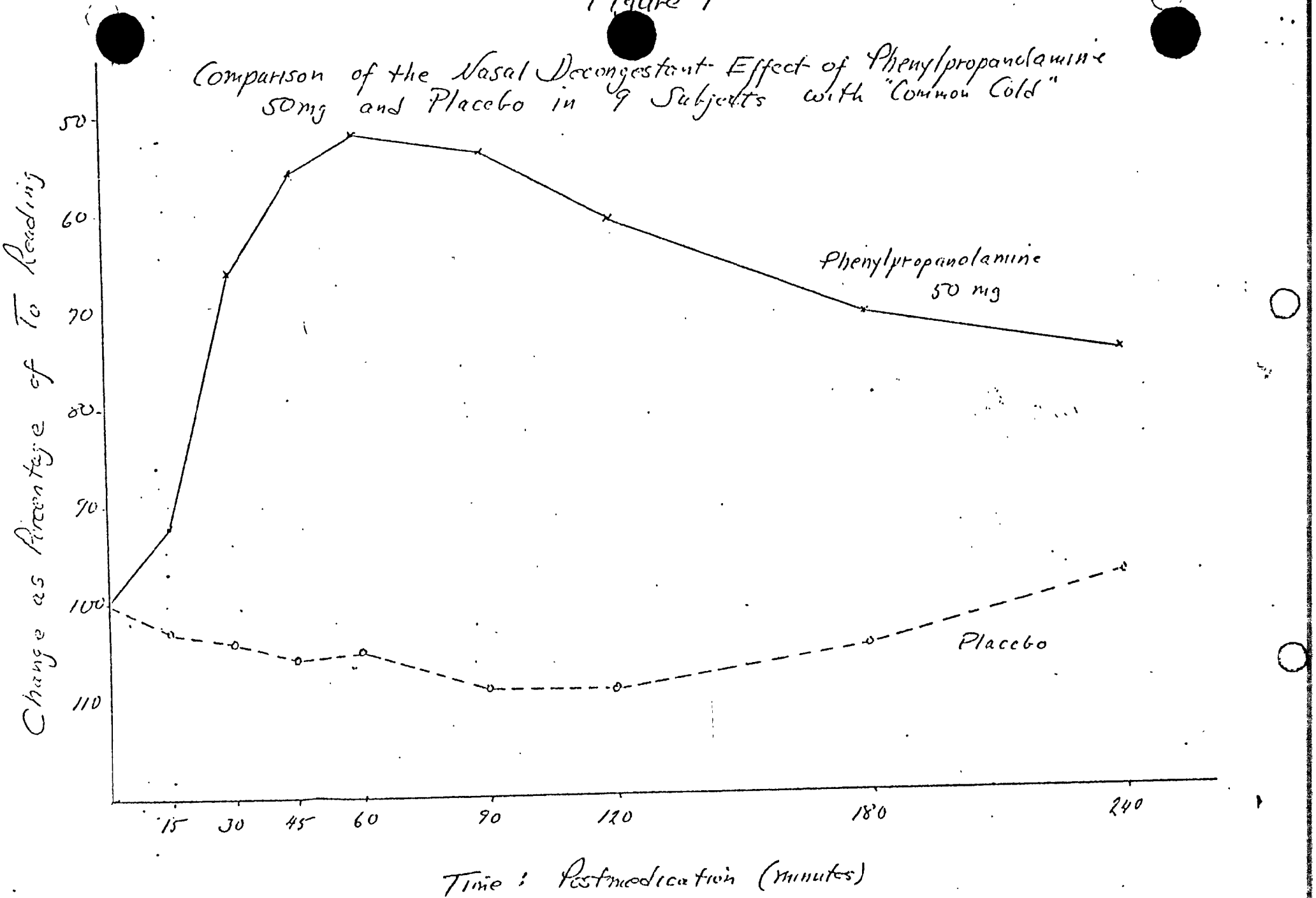

Comparison of the Nasal Decongestant Effect of Phenylpropanolamine 50mg and Placebo in 9 Subjects with "Common Cold"
Change as Percentage of To Reading
50
60
70
80
90
100
110
Phenylpropanolamine 50 mg
Placebo
15
30
45
60
90
120
180
240
Time: Postmedication (minutes)

Figure 2

Comparison of the Nasal Decongestant Effect of Oral Neo-Synephrine 5mg and Placebo in 16 Subjects with "Common Cold"

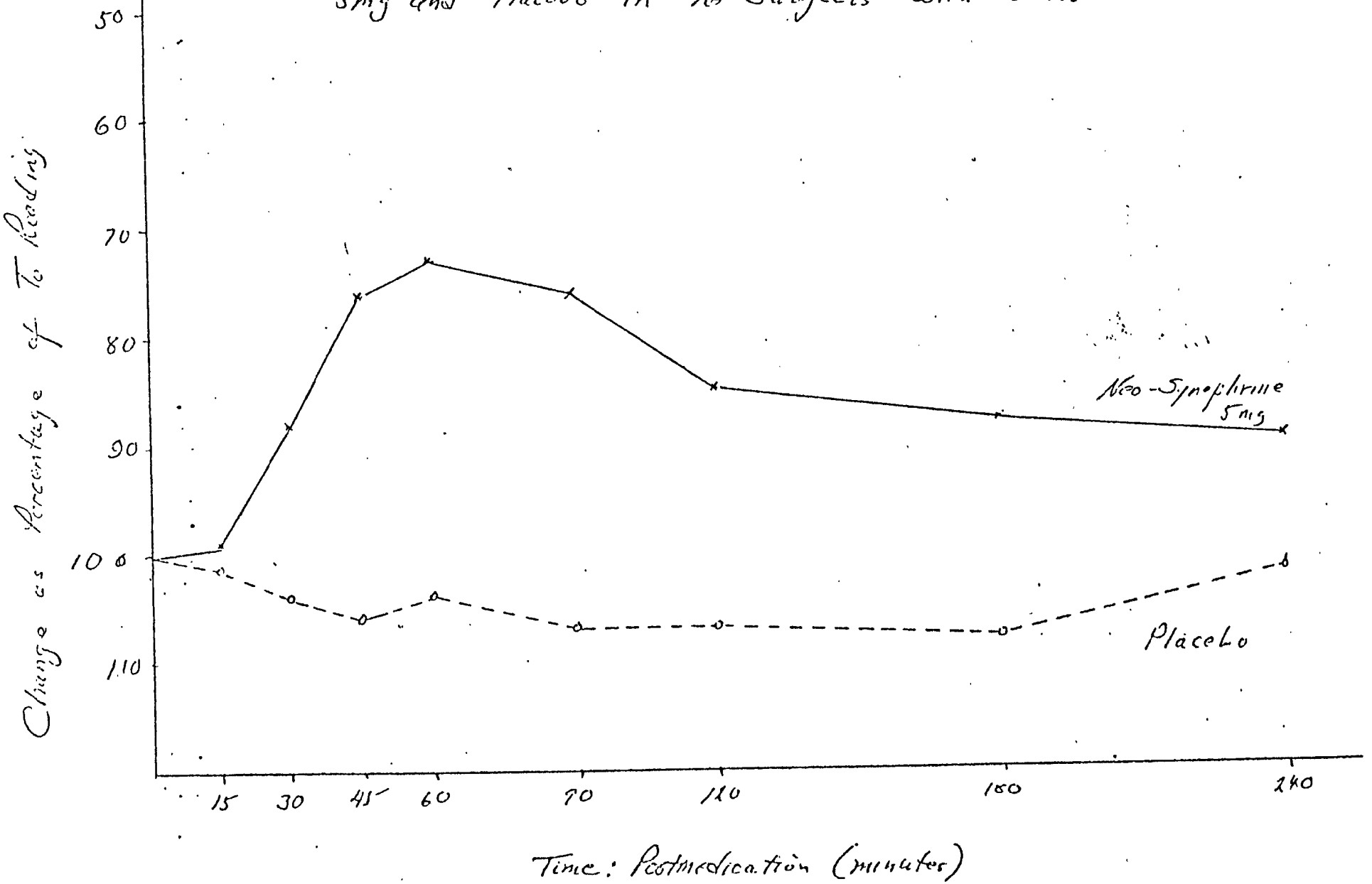


Figure 3

Comparison of the Nasal Decongestant Effect of Oral Neo-Synephrine 15mg and Placebo in 8 Subjects with Common Cold

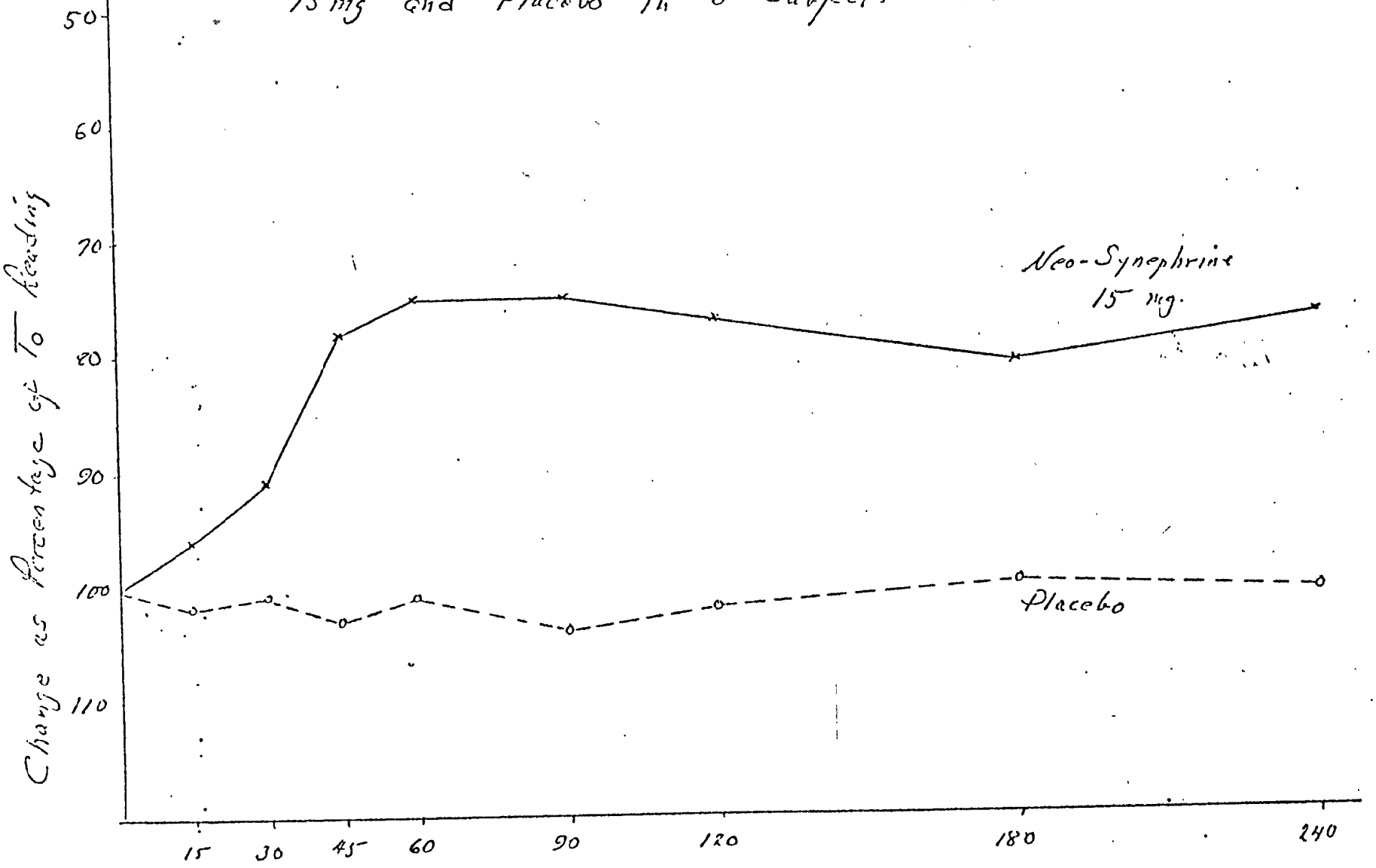
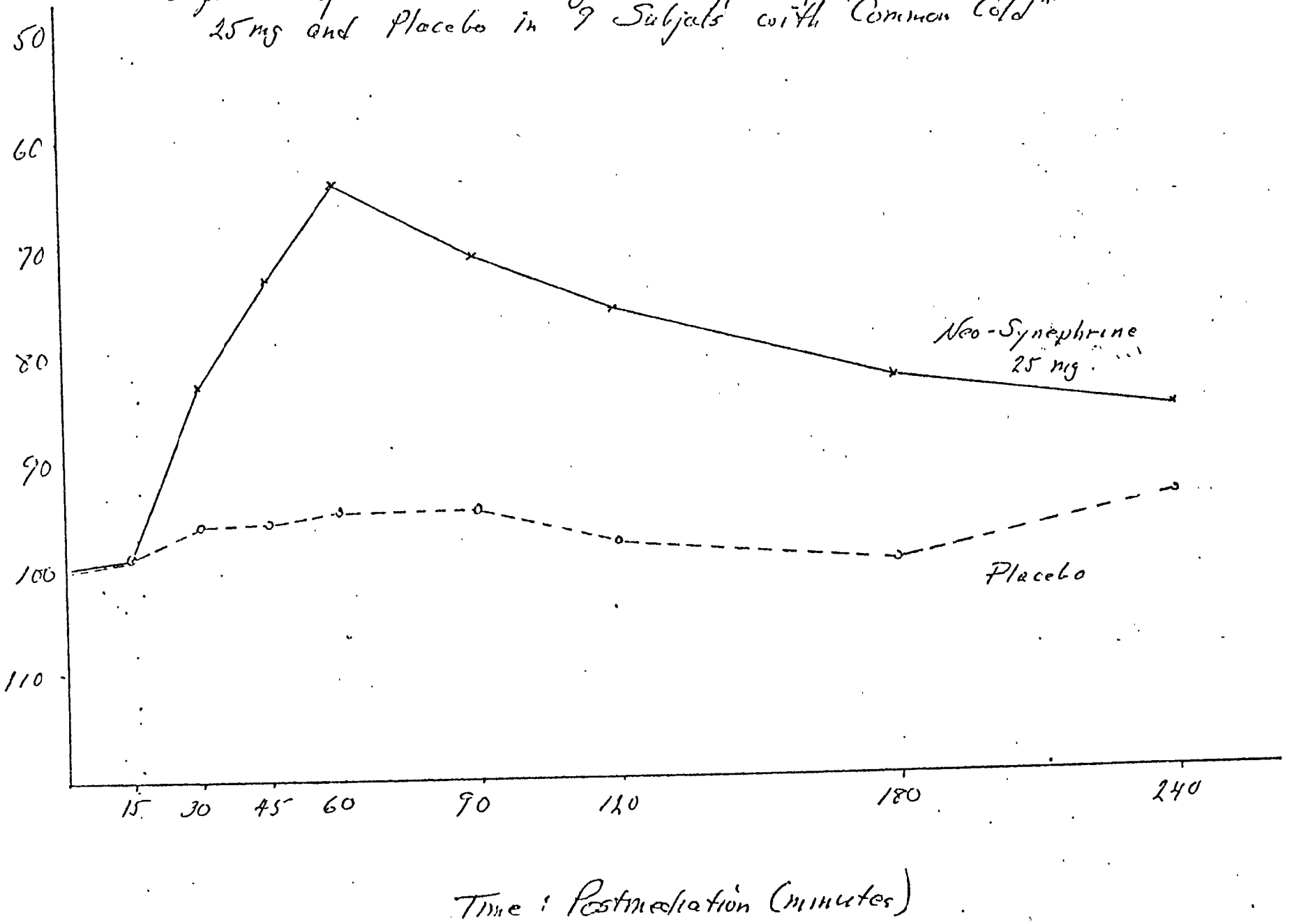


Figure 4

Comparison of the Nasal Decongestant Effect of Oral Neo-Synephrine 25 mg and Placebo in 9 Subjects with "Common Cold"



APPENDIX

Objective Measurement Means* Neo-Synephrine (5 mg)

Patient	Treatment	t_0**	t_{15}***	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}	t_{180}	t_{240}
3	Drug	11.6	1.09	1.02	0.95	0.81	0.78	0.96	1.02	1.12
	Placebo	11.0	1.09	1.12	1.14	1.16	1.10	1.14	1.19	1.21
5	Drug	12.5	1.02	0.90	0.65	0.43	0.55	0.76	0.72	0.52
	Placebo	11.2	1.04	1.08	1.14	1.20	1.25	1.07	1.12	0.96
7	Drug	11.3	1.02	1.02	0.74	0.74	0.79	0.82	0.93	1.06
	Placebo	13.0	0.95	0.95	1.02	0.99	1.04	1.01	1.01	0.96
8	Drug	12.3	0.98	0.77	0.72	0.93	0.97	0.98	1.00	1.15
	Placebo	13.2	0.95	0.95	1.04	0.92	0.91	0.93	0.97	0.86
9	Drug	15.4	0.89	0.82	0.63	0.65	0.64	0.71	0.58	0.52
	Placebo	10.5	0.90	0.97	1.06	1.00	0.95	1.08	1.05	1.03
12	Drug	11.5	0.94	0.82	0.65	0.81	0.87	0.88	0.96	1.00
	Placebo	11.7	1.00	1.00	1.00	1.01	1.00	1.01	1.01	0.98
16	Drug	15.5	0.96	0.84	0.83	0.70	0.74	0.72	0.75	0.80
	Placebo	12.0	0.95	1.02	1.00	1.04	1.04	1.06	1.00	0.90
18	Drug	10.1	1.04	0.86	0.73	0.77	0.89	0.98	1.17	1.26
	Placebo	13.7	1.06	1.06	1.09	1.09	1.12	1.05	1.05	1.02
22	Drug	11.2	1.01	0.88	0.70	0.71	0.67	0.76	0.74	0.82
	Placebo	10.7	1.07	1.09	1.06	1.09	1.13	1.11	1.07	1.06
24	Drug	12.5	0.97	0.86	0.89	0.84	0.70	0.92	0.93	0.84
	Placebo	11.5	1.04	1.01	1.04	1.02	1.14	1.12	1.16	1.17
34	Drug	12.5	0.98	0.90	0.84	0.88	0.94	1.00	0.93	0.92
	Placebo	11.6	1.02	1.06	1.02	0.78	0.96	0.99	1.06	0.98
36	Drug	11.5	1.02	1.00	0.90	0.65	0.78	0.87	0.87	0.86
	Placebo	12.0	0.96	1.04	1.04	1.02	1.06	1.06	0.95	0.92
39	Drug	12.0	0.96	0.96	0.97	0.63	0.79	0.88	0.91	0.92
	Placebo	11.7	1.08	1.07	1.11	1.06	1.07	1.05	1.14	1.06
41	Drug	15.5	0.99	0.97	0.72	0.74	0.74	0.81	0.82	0.71
	Placebo	14.0	0.98	1.04	1.07	1.07	1.07	1.07	1.02	0.98
44	Drug	15.2	0.98	0.82	0.66	0.53	0.56	0.80	0.84	0.95
	Placebo	13.7	0.97	0.98	1.06	1.09	1.06	1.06	1.06	0.98
46	Drug	14.4	1.01	0.62	0.63	0.80	0.69	0.75	0.97	1.01
	Placebo	10.3	1.12	1.14	1.02	1.08	1.22	1.31	1.34	1.31

*Each number represents the mean of 5 measurements on both right and left nostrils.

t_0: premedication reading (units) *t_{15}, etc.: mean as % of t_0

APPENDIX

Objective Measurement Means*
Neo-Synephrine (15 mg)

Patient	Treatment	t_0**	t_{15}***	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}	t_{180}	t_{240}
6	Drug	19.3	0.96	1.01	1.04	1.00	0.99	1.02	0.90	0.70
	Placebo	15.7	0.99	0.97	0.96	0.92	0.92	0.98	0.99	1.18
10	Drug	11.6	0.96	0.85	0.60	0.61	0.65	0.72	0.72	0.61
	Placebo	10.9	1.02	1.02	1.07	1.06	1.16	1.11	1.10	1.10
20	Drug	11.5	0.96	0.90	0.77	0.64	0.63	0.60	0.52	0.49
	Placebo	10.5	1.08	1.10	1.11	1.06	1.08	1.08	1.10	0.98
23	Drug	11.5	1.00	0.78	0.74	0.65	0.71	0.83	0.91	0.96
	Placebo	11.1	1.13	1.05	1.13	1.08	1.05	1.04	0.96	0.81
27	Drug	15.4	0.97	0.94	0.75	0.68	0.72	0.79	0.82	0.88
	Placebo	15.3	1.04	1.03	1.02	1.05	1.01	1.01	1.01	1.04
31	Drug	12.0	0.96	0.98	0.74	0.66	0.73	0.74	0.88	1.02
	Placebo	12.0	0.99	1.00	1.02	1.04	1.09	1.05	0.92	1.08
40	Drug	13.4	0.89	0.98	0.93	1.01	0.81	0.58	0.82	0.55
	Placebo	13.6	0.96	0.96	0.95	0.91	1.00	0.95	0.93	0.85
45	Drug	15.8	0.95	0.83	0.71	0.72	0.75	0.90	0.89	0.97
	Placebo	15.5	0.97	0.98	1.01	0.97	1.05	0.93	1.02	1.05

*Each number represents the mean of 5 measurements on both right and left nostrils.

t_0: premedication reading (units) *t_{15}, etc.: mean as % of t_0

APPENDIX

Objective Measurement Means*
Neo-Synephrine (25 mg)

Patient	Treatment	t_0**	t_{15}***	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}	t_{180}	t_{240}
11	Drug	13.0	0.84	0.61	0.45	0.47	0.55	0.70	0.72	0.62
	Placebo	14.5	1.03	1.03	1.03	0.97	1.03	1.03	1.11	0.92
13	Drug	10.8	1.08	1.06	1.03	1.08	1.10	1.13	1.28	1.34
	Placebo	14.9	0.93	0.53	0.53	0.37	0.41	0.54	0.55	0.83
15	Drug	13.9	0.96	0.65	0.54	0.53	0.65	0.61	0.68	0.79
	Placebo	15.5	0.99	0.97	0.96	0.96	0.99	1.01	0.92	0.82
21	Drug	11.5	0.99	0.62	0.57	0.55	0.65	0.63	0.73	0.74
	Placebo	11.5	1.02	1.03	0.96	1.03	1.07	1.01	1.03	1.00
29	Drug	20.7	1.02	0.99	1.01	0.71	0.80	0.89	0.85	0.80
	Placebo	11.3	0.96	1.00	0.98	0.96	0.98	0.99	1.28	1.17
30	Drug	14.3	1.05	1.02	1.07	0.71	0.71	0.76	0.71	0.64
	Placebo	14.1	1.06	1.06	1.07	1.10	1.10	1.08	1.09	0.82
32	Drug	12.0	0.99	1.02	0.75	0.58	0.74	0.79	0.88	0.97
	Placebo	12.0	1.00	0.99	1.02	1.08	1.12	1.12	1.00	1.05
38	Drug	15.5	0.94	0.55	0.44	0.39	0.48	0.51	0.65	0.87
	Placebo	12.8	0.90	0.94	1.07	0.99	0.75	0.84	0.89	0.90
43	Drug	13.5	1.07	0.99	0.70	0.79	0.75	0.82	0.96	0.93
	Placebo	12.0	1.04	1.10	1.04	1.06	1.12	1.16	1.12	0.98

*Each number represents the mean of 5 measurements on both right and left nostrils.

t_0: premedication reading (units) *t_{15}, etc.: mean as % of t_0

APPENDIX

Objective Measurement Means*
Phenylpropanolamine (50 mg)

Patient	Treatment	t_0**	t_{15}***	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}	t_{180}	t_{240}
1	Drug	14.5	0.83	0.54	0.46	0.46	0.43	0.43	0.85	0.95
	Placebo	12.9	1.03	1.04	1.02	1.03	1.03	1.00	0.93	1.00
2	Drug	15.3	0.88	0.81	0.59	0.43	0.39	0.39	0.38	0.39
	Placebo	12.6	1.02	1.01	1.04	0.91	1.23	1.15	1.15	0.98
4	Drug	14.5	0.99	0.74	0.57	0.59	0.52	0.38	0.41	0.38
	Placebo	11.5	1.00	1.02	1.04	1.03	1.08	1.09	0.98	0.77
14	Drug	13.7	0.98	0.51	0.44	0.38	0.51	0.58	0.69	0.60
	Placebo	11.9	0.98	1.01	0.95	1.01	1.02	1.08	1.00	1.01
17	Drug	11.4	1.02	0.83	0.81	0.56	0.53	0.66	0.67	1.08
	Placebo	10.0	1.17	1.21	1.30	1.31	1.19	1.24	1.19	1.03
19	Drug	10.4	0.82	0.55	0.64	0.55	0.63	0.76	0.86	0.88
	Placebo	10.9	1.02	1.04	1.06	1.11	1.11	1.09	1.06	0.96
28	Drug	12.0	0.92	0.62	0.51	0.59	0.59	0.72	0.92	0.88
	Placebo	14.4	0.97	0.98	0.97	1.00	1.03	1.03	0.92	0.97
37	Drug	12.6	0.90	0.60	0.56	0.72	0.77	0.92	0.87	0.91
	Placebo	11.9	1.05	1.06	1.14	0.98	1.05	1.10	1.14	1.06
42	Drug	15.1	0.90	0.76	0.50	0.39	0.46	0.67	0.77	0.69
	Placebo	14.5	1.05	1.03	1.01	1.07	1.07	1.04	1.11	1.03

*Each number represents the mean of 5 measurements on both right and left nostrils.

t_0: premedication reading (units) *t_{15}, etc: mean as % of t_0

REFERENCE 17

INTER-OFFICE MEMORANDUM

STERLING-WINTHROP RESEARCH INSTITUTE

RENSSELAER, NEW YORK

C.F.

August 11, 1969

Ref #9

To: Dr. Blackmore

From: N. A. Hulme

Re: Oral Neo-Synephrine - Elizabeth Biochemical Study No. 4

In order to expand the previous data and to extend the studies into decongestant dosages of greater potential interest a study was conducted at Elizabeth Biochemical Labs in which decongestant and cardiovascular effects were monitored in subjects administered 15, 20 or 25 mg capsules of Neo-Synephrine.

The study as originally conceived was not completed in its entirety because of the lack of sufficient cold subjects coincidental with the arrival of warmer weather in the spring. Preliminary analysis of the available data; however, indicated that differencesbetween placebo and active medication were sufficiently great to permit a full statistical analysis of reports. It was decided therefore to report out the data at hand rather than to have it divided into two segments.

The following discussion and data are based on a statistical analysis of the results as provided by Mr. Stander.

Protocol and Methodology

A total of 20 subjects with head colds and having confirmed nasal congestion on two consecutive days participated in the study. Evaluation of the degree of nasal congestion was made by measuring the relative resistance to a constant flow of air passing through the nasal passageway by a modification of the Butler-Ivy procedure (Blanchard et al E.E.N.T. Monthly 43, 76-82, 1964).

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The subjects were assigned coded drugs on a double-blind randomized basis. The randomization was designed so that half the subjects in each dose category received placebo on the first day and active medication on the second day. The reversed sequence occurred with the other subjects. The following table gives the number of subjects receiving each of the drugs.

15-25

No. of Subjects	Neo-Synephrine vs. Placebo
6	15 mg
5	20 mg
9	25 mg

All drugs were supplied in identical capsules and packaged in individual preassigned envelopes labeled by code number and subject number.

Objective measurements of airflow resistance were carried out by obtaining five consecutive readings for each nostril at 0, 15 and 30 minutes before medication and 15, 30, 45, 60, 120 and 240 minute intervals following medication. The ten readings from both nostrils were combined and the arithmetic means employed for further calculations and analysis.

Subjective impressions of changes in nasal congestion were obtained by having each subject describe his congestion at the time each set of airflow measurements were made. These were classified as being closest to one of the following conditions:

Degree of Congestion
Nose feels clear
Almost clear
Stuffy
Very stuffy
Completely blocked

A shift of one degree of congestion from the premedication state was graded as plus or minus 1, a shift in two degrees as plus or minus 2, etc. The sums of the change at each time interval were recorded for each subject. The median change for all subjects on each active medication dosage was compared to the same subject's placebo scores for significance of the difference.

Pulse and sitting blood pressure readings were obtained on each subject at 30, 15 and 0 minutes before medication and at 30, 60, 90, 120, 180, and 240 minutes following medication. The readings from each medication group were combined and the arithmetic means employed for further calculations and analysis. This provided comparisons between active medication and placebo for diastolic pressure, systolic pressure and pulse rate.

Results

The individual subject's air resistance measurement figures (see Appendix) were used to calculate arithmetic differences between premedication and postmedication results at indicated specific time intervals. These data were analyzed by Mr. Stander's group for significance between the placebo and medication readings. The mean values and the degree of significance at each of the dosages are given in Table I. These data are plotted as graphs for each dosage:placebo pair in Figures 1 to 3.

These data show significant differences occurring between placebo and all three dosages of Neo-Synephrine. The onset of significant divergence between placebo and active medication occurred at the 45 minute reading with all three dosages. The duration of period of significance difference lasted until the 120 minute reading at the 15 mg dose, the 240 minute reading at 20 mg and the 180 minute reading with the 25 mg dose.

The analysis of the scores for the subjective impressions of decongestion showed a positive correlation for subjects receiving the 20 mg dose, possibly significant correlation at the 15 mg dose and no correlation for subjects on the 25 mg dose. The failure to show correlation at the latter dose may be due to the relatively small number of subjects.

Analysis of the pulse rate data showed no changes of significance in subjects receiving the 15 mg dose. Periods of significant difference in subjects when given placebo and when receiving 20 mg Neo-Synephrine occurred at the 120 and 180 minute time intervals and when subjects received 25 mg Neo-Synephrine at the 180 minute interval. The clinical significance of the changes is questionable in that the direction of change in subjects receiving active medication is opposite to that expected, that is, there was a numerical increase in pulse rate rather a decrease as would be expected from a true drug effect.

Analysis of the systolic blood pressure data showed no (NONE) significant differences occurring between placebo and Neo-Synephrine 15, 20, or 25 mg at any of the postmedication time periods. The same was seen in regard to the diastolic pressure with one exception which occurred at a single time period in subjects given the 25 mg dose. Again the effect was that of a relative drop in diastolic blood pressure while on active drug as compared to placebo and must be considered an aberrant effect and not a true drug effect.

Discussion

This study although a small one brings in positive correlative data from a third laboratory on the decongestant effect of Neo-Synephrine at a 20 mg dose. In addition cardiovascular data on actual patients with head colds was obtained and so provides much needed data in this category.

N. A. Hulme

bjc
Attachments

cc: Dr. Wessinger
Dr. Luduena
Mr. Stander
Dr. Cox
Dr. Surrey
Mr. Heike
Dr. Gerding
Dr. Rees
Dr. Giambalvo
File

Table I

COMPARISON OF THE NASAL DECONGESTANT EFFECT OF ORAL NEO-SYNEPHRINE (15 mg, 20 mg, 25 mg) VERSUS PLACEBO IN SUBJECTS WITH COMMON COLD

Objective Measurements (fractional units)

	t_0	t_{15}/t_0	t_{30}/t_0	t_{45}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0	t_{180}/t_0	t_{240}/t_0
Neo-Synephrine 15 mg	12.0	.97	.99	.83	.78	.83	.82	.95	1.02
Placebo	12.9	1.01	1.01	.98	.97	.99	1.00	1.01	1.03
Analysis of Variance (s) (n = 6)	p>0.05 s=0.82	p>0.05 s=0.04	p>0.05 s0.03	p=0.05 s=0.07	p=0.10 s=0.18	p≅0.05 s=0.12	p≅0.05 s=0.15	p>0.05 s=0.08	p>0.05 s=0.05
Neo-Synephrine 20 mg	13.8	.96	.93	.73	.68	.63	.69	.76	.85
Placebo	12.1	1.00	1.00	1.02	1.06	1.07	1.07	1.02	.97
Analysis of Variance (s) (n = 5)	p>0.05 s=2.22	p>0.05 s=0.07	p>0.05 s=0.08	p=0.01 s=0.07	p=0.01 s=0.20	p=0.01 s=0.17	p=0.01 s=0.17	p=0.01 s=0.09	p=0.01 s=0.05
Neo-Synephrine 25 mg	12.9	1.00	.97	.76	.73	.77	.81	.83	.95
Placebo	13.4	1.00	1.00	1.00	1.00	.99	1.02	.97	.95
Analysis of Variance (s) (n = 9)	p>0.05 s=0.99	p>0.05 s=0.03	p>0.05 s=0.06	p=0.01 s=0.14	p=0.01 s=0.17	p=0.01 s=0.13	p=0.01 s=0.15	p=0.01 s=0.12	p>0.05 s=0.07

Table II

COMPARISON OF THE NASAL DECONGESTANT EFFECT OF ORAL NEO-SYNEPHRINE (15 mg, 20 mg, 25 mg) VERSUS PLACEBO IN SUBJECTS WITH COMMON COLD

Subjective Impression Differences

	Median Differences	Analysis of Variance	Standard Deviation	Number of Subjects
Neo-Synephrine 15 mg	-6.7	p=0.10	1.37	6
Placebo	-4.5			
Neo-Synephrine 20 mg	-7.2	p=0.05	2.08	5
Placebo	-4.4			
Neo-Synephrine 25 mg	-5.8	p>0.10	2.42	9
Placebo	-7.2			

Table III

COMPARISON OF THE EFFECT OF ORAL NEO-SYNEPHRINE (15 mg, 20 mg, 25 mg) ON THE PULSE RATE IN SUBJECTS WITH COMMON COLD

(Fractional Units of t_0 Readings)

	t_0	t_{30}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0	t_{180}/t_0	t_{240}/t_0
Neo-Synephrine 15 mg	79.3	.99	1.00	1.00	1.02	1.03	1.02
Placebo	79.7	.97	.99	.98	.98	1.00	1.02
Analysis of Variance (s) (n = 6)	p>0.05 s=2.27	p>0.05 s=0.018	p>0.05 s=0.036	p>0.05 s=0.053	p>0.05 s=0.052	p>0.05 s=0.027	p>0.05 s=0.044
Neo-Synephrine 20 mg	76.0	1.01	.99	.99	1.02	1.04	1.01
Placebo	78.4	.98	.96	.97	.94	.93	.94
Analysis of Variance (s) (n = 5)	p>0.05 s=3.22	p>0.05 s=0.041	p>0.05 s=0.041	p>0.05 s=0.049	p=0.05 s=0.038	p=0.01 s=0.044	p>0.05 s=0.036
Neo-Synephrine 25 mg	82.2	.99	.98	.98	.99	1.01	1.00
Placebo	78.7	.97	.99	.99	1.01	.96	.98
Analysis of Variance (s) (n = 9)	p>0.05 s=4.23	p>0.05 s=0.056	p>0.05 s=0.042	p>0.05 s=0.049	p>0.05 s=0.069	p≅0.05 s=0.076	p>0.05 s=0.010

Table IV

COMPARISON OF THE EFFECT OF ORAL NEO-SYNEPHRINE (15 mg, 20 mg, 25 mg) ON THE SYSTOLIC BLOOD PRESSURE IN SUBJECTS WITH COMMON COLD

(Fractional Units of t_0 Readings)

	t_0	t_{30}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0	t_{180}/t_0	t_{240}/t_0
Neo-Synephrine 15 mg	138	1.00	1.00	1.01	1.01	1.01	1.01
Placebo	139	.98	.99	.99	.99	.99	.99
Analysis of Variance (s) (n = 6)	p>0.05 s=1.06	p>0.05 s=0.02	p>0.05 s=0.02	p>0.05 s=0.03	p>0.05 s=0.02	p>0.05 s=0.01	p>0.05 s=0.02
Neo-Synephrine 20 mg	142	.99	.99	1.00	1.01	1.00	.99
Placebo	140	.99	.99	.99	.99	.99	.99
Analysis of Variance (s) (n = 5)	p>0.05 s=3.32	p>0.05 s=0.02	p>0.05 s=0.02	p>0.05 s=0.03	p>0.05 s=0.02	p>0.05 s=0.01	p>0.05 s=0.02
Neo-Synephrine 25 mg	142	1.00	1.00	.99	1.00	1.01	1.00
Placebo	142	1.00	1.02	1.02	1.03	1.02	1.03
Analysis of Variance (s) (n = 9)	p>0.05 s=2.55	p>0.05 s=0.03	p>0.05 s=0.04	p>0.05 s=0.05	p>0.05 s=0.06	p>0.05 s=0.05	p>0.05 s=0.08

Table V

COMPARISON OF THE EFFECT OF ORAL NEO-SYNEPHRINE (15 mg, 20 mg, 25 mg) ON THE DIASTOLIC BLOOD PRESSURE IN SUBJECTS WITH COMMON COLD

(Fractional Units of t_0 Readings)

	t_0	t_{30}/t_0	t_{60}/t_0	t_{90}/t_0	t_{120}/t_0	t_{180}/t_0	t_{240}/t_0
Neo-Synephrine 15 mg	84.0	1.01	1.00	1.00	1.00	1.01	.99
Placebo	84.7	.97	1.00	1.02	1.02	.99	1.01
Analysis of Variance (s) (n = 6)	p>0.05 s=2.92	p>0.05 s=0.04	p>0.05 s=0.05	p>0.05 s=0.07	p>0.05 s=0.08	p>0.05 s=0.07	p>0.05 s=0.03
Neo-Synephrine 20 mg	80.4	1.00	1.01	1.00	1.02	1.02	1.00
Placebo	82.0	1.00	.98	.98	.97	.96	.95
Analysis of Variance (s) (n = 5)	p>0.05 s=2.10	p>0.05 s=0.03	p>0.05 s=0.03	p>0.05 s=0.04	p>0.05 s=0.03	p>0.05 s=0.03	p>0.05 s=0.04
Neo-Synephrine 25 mg	81.3	.98	.97	.96	.96	.96	.96
Placebo	83.1	1.00	1.01	1.00	1.03	1.00	1.01
Analysis of Variance (s) (n = 9)	p>0.05 s=2.05	p>0.05 s=0.04	p>0.05 s=0.03	p>0.05 s=0.04	p=0.05 s=0.05	p>0.05 s=0.07	p>0.05 s=0.08

Figure 1

Comparison of the Nasal Decongestant Effect of Neo-Synephrine 15mg and Placebo in 6 Subjects with Common Cold

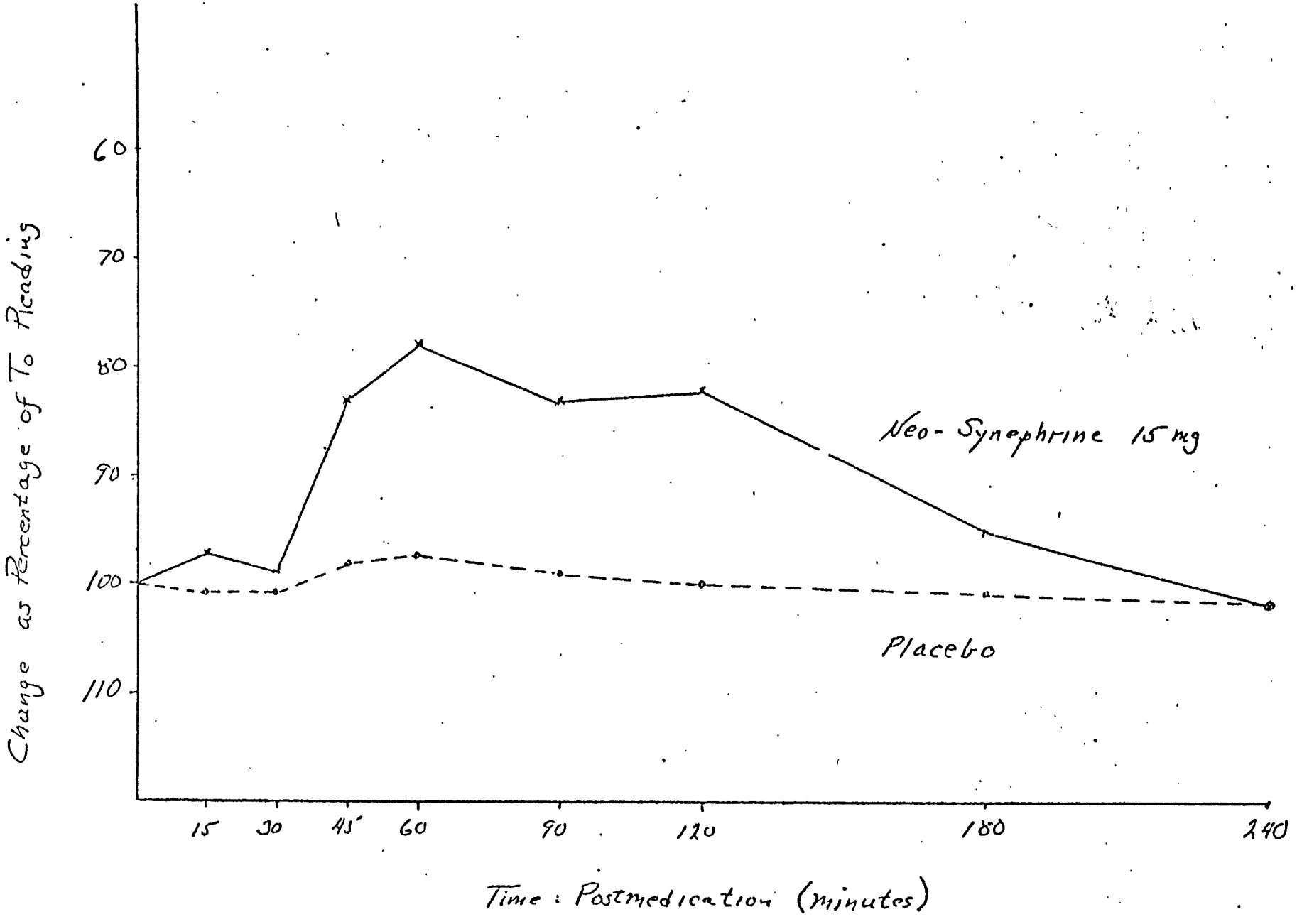


Fig. 2

Comparison of the Nasal Decongestant Effect of Oral Neo-Synephrine 20mg and Placebo in 5 Subjects with Common Cold

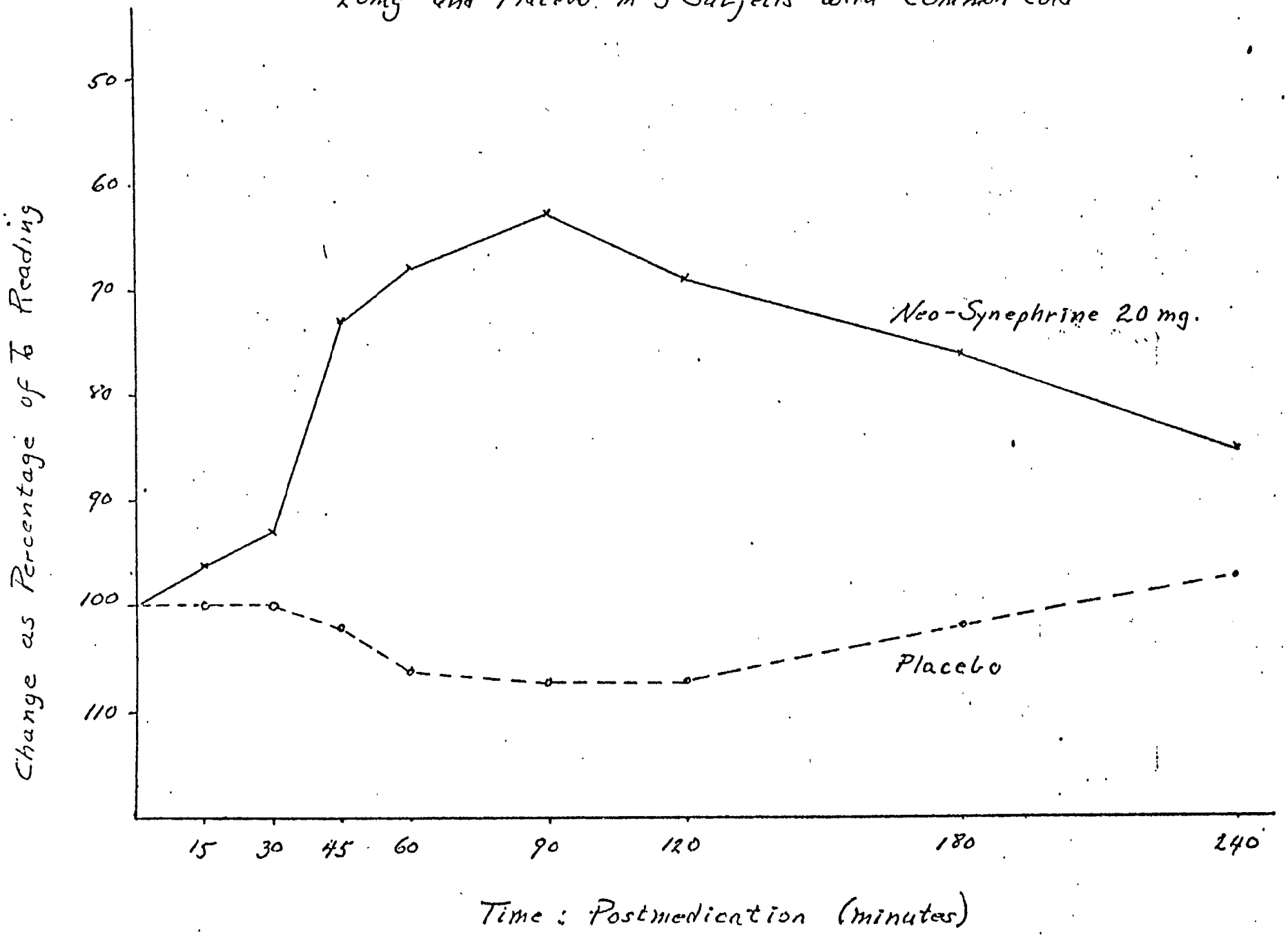
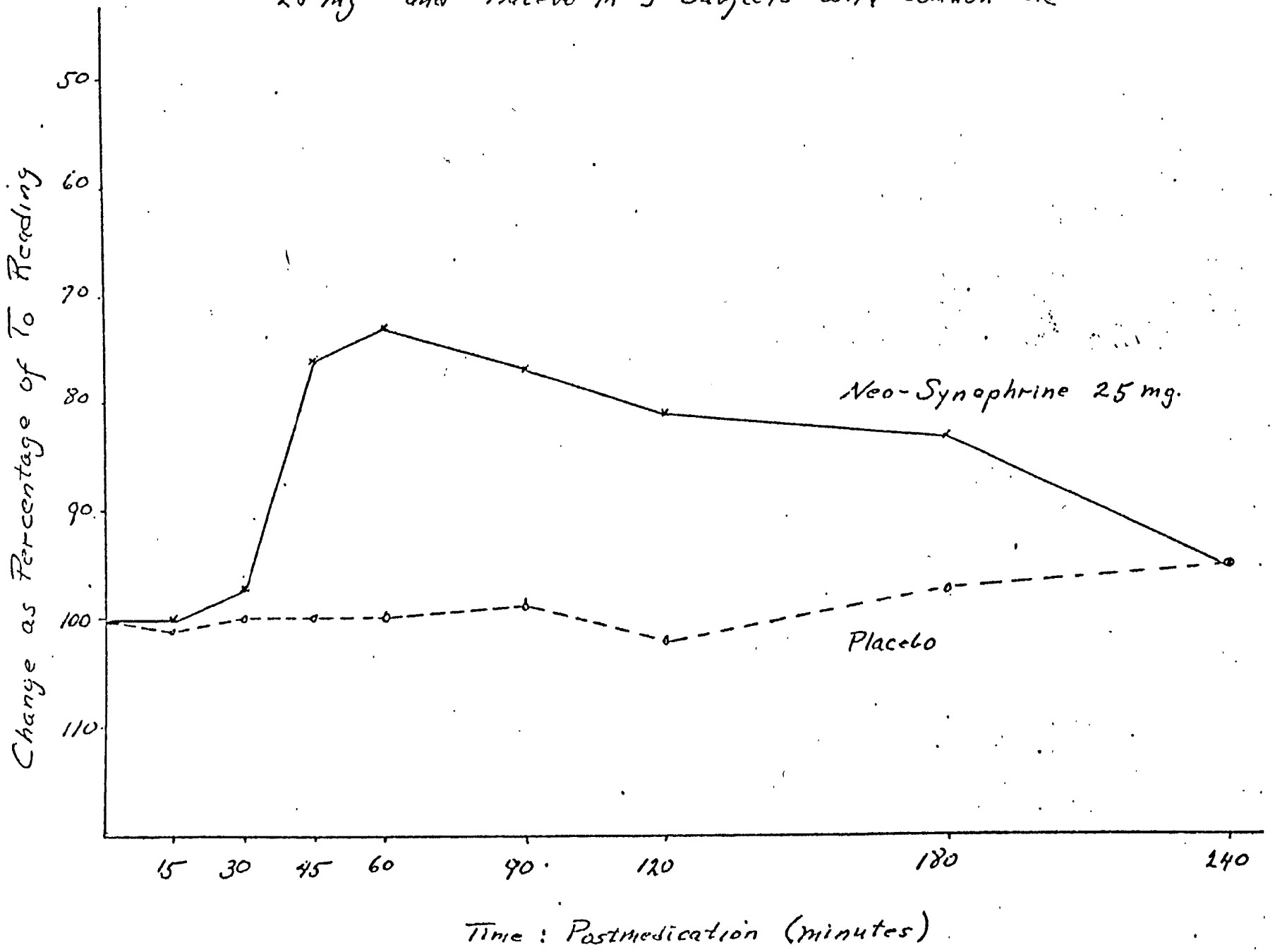


Figure 3

Comparison of the Nasal Decongestant Effect of Oral Neo-Synephrine 25 mg and Placebo in 9 Subjects with Common Cold



APPENDIX

Objective Measurement Means*
Neo-Synephrine (15 mg)

Patient	Treatment	t_0**	t_{15}***	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}	t_{180}	t_{240}
3	Drug	10.7	0.97	0.96	0.83	0.99	0.99	1.00	1.03	1.07
	Placebo	11.3	1.01	1.00	0.93	0.95	0.97	0.97	1.04	1.02
6	Drug	10.7	0.90	0.91	0.77	0.93	0.90	0.93	1.02	1.00
	Placebo	10.3	0.96	0.99	0.98	0.91	0.96	0.96	0.96	0.98
7	Drug	10.4	0.92	1.01	0.95	0.63	0.71	0.52	0.93	1.02
	Placebo	11.7	1.03	1.03	0.98	1.00	1.03	1.04	1.08	1.09
9	Drug	11.3	1.01	0.99	0.66	0.84	0.99	0.99	1.00	1.05
	Placebo	12.5	0.98	1.01	0.98	1.00	1.00	1.04	0.99	1.01
10	Drug	14.5	1.01	1.03	0.86	0.55	0.58	0.62	0.77	1.00
	Placebo	13.7	0.98	0.99	1.01	0.96	0.97	0.97	1.00	0.99
20	Drug	14.7	0.99	1.05	0.91	0.75	0.78	0.84	0.94	0.97
	Placebo	17.4	1.09	1.03	1.02	1.01	1.02	1.03	1.01	1.07

*Each number represents the mean of 5 measurements on both right and left nostrils.

t_0: premedication reading (units) *t_{15}, etc.: Mean as % of t_0

APPENDIX

Objective Measurement Means*
Neo-Synephrine (20 mg)

Patient	Treatment	t_0**	t_{15}***	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}	t_{180}	t_{240}
4	Drug	18.3	0.93	0.93	0.81	1.02	0.96	1.04	0.90	0.82
	Placebo	11.5	1.00	1.02	1.01	1.02	1.03	1.03	1.10	1.05
8	Drug	13.6	1.01	1.00	0.80	0.45	0.47	0.65	0.69	0.77
	Placebo	14.5	1.06	1.01	1.06	1.24	1.24	1.22	1.03	0.90
12	Drug	14.4	0.99	0.96	0.72	0.63	0.62	0.65	0.76	0.76
	Placebo	11.7	1.03	1.02	1.06	1.02	1.05	1.07	1.02	0.86
14	Drug	11.2	0.83	0.75	0.78	0.79	0.63	0.56	0.67	0.97
	Placebo	10.5	1.00	1.00	0.98	1.00	1.10	1.13	1.10	1.10
18	Drug	11.7	1.05	1.02	0.56	0.50	0.47	0.52	0.77	0.90
	Placebo	12.2	0.94	0.96	1.00	1.01	0.94	0.90	0.88	0.94

*Each number represents the mean of 5 measurements on both right and left nostrils.

t_0: premedication reading (units) *t_{15}, etc: mean as % of t_0

APPENDIX

Objective Measurement Means*
Neo-Synephrine (25 mg)

Patient	Treatment	t_0**	t_{15}***	t_{30}	t_{45}	t_{60}	t_{90}	t_{120}	t_{180}	t_{240}
1	Drug	10.5	1.09	0.96	0.66	1.08	1.11	1.06	1.08	1.05
	Placebo	12.5	1.09	1.16	1.19	1.27	1.26	1.34	1.24	1.13
2	Drug	11.4	0.99	1.01	0.79	0.61	0.61	0.66	0.48	1.04
	Placebo	14.6	1.00	1.07	1.07	1.13	1.00	1.23	0.97	0.92
5	Drug	10.9	1.05	0.99	0.65	0.77	0.87	0.78	0.83	0.97
	Placebo	10.3	1.09	1.06	1.12	0.92	1.00	1.00	1.01	1.07
11	Drug	11.5	1.02	0.97	0.73	1.01	0.86	0.99	1.02	0.89
	Placebo	10.8	0.91	0.90	0.79	0.81	0.83	0.96	0.97	0.95
13	Drug	12.5	0.98	1.02	1.02	0.98	1.08	1.08	0.96	0.98
	Placebo	12.8	1.02	0.99	1.01	1.04	1.01	0.94	0.91	0.89
15	Drug	12.5	0.99	0.95	0.95	0.43	0.48	0.63	0.82	0.84
	Placebo	14.0	0.95	0.89	0.93	0.97	0.93	0.97	0.96	0.89
16	Drug	19.2	1.01	0.94	0.72	0.60	0.59	0.63	0.72	1.02
	Placebo	19.4	1.01	1.00	0.99	0.96	0.96	0.91	0.86	0.86
17	Drug	15.4	0.95	0.94	0.62	0.52	0.60	0.68	0.71	0.88
	Placebo	14.7	0.97	0.97	0.98	0.93	0.95	0.97	0.92	0.92
19	Drug	12.4	0.94	0.97	0.70	0.52	0.69	0.76	0.87	0.93
	Placebo	12.0	0.96	0.97	0.94	0.98	0.97	0.84	0.92	0.96

*Each number represents the mean of 5 measurements on both right and left nostrils.

t_0: premedication reading (units) *t_{15}, etc.: mean as % of t_0

REFERENCE 18

Eccles, R., M. S. M. Jawad, S. S. M. Jawad, J. T. Angelo, and H. M. Druce, "Efficacy and Sasfety of Single and Multiple Doses of Pseudoepedrine in the Treatment of Nasal Congestion Associated with Common Cold," *American Journal of Rhinology* 19:25-31, 2005.

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Schumacher, M. J., “Nasal Dyspnea: The Place of Rhinomanometry in its Objective Assessment,” *American Journal of Rhinology* 18:41-46, 2004.

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Keys, A. and A. Violante, “The Cardio-Circulatory Effects in Man of Neo-Synephrin (1-alpha-hydroxy-beta-methylamino-3-hydroxy-ethylbenzene hydrochloride),” *Journal of Clinical Investigation* 21:1-12, 1942

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INTER-OFFICE MEMORANDUM

STERLING-WINTHROP RESEARCH INSTITUTE

RENSSELAER, NEW YORK

Vol. 169 IV-1

Reference # 2

June 19, 1968

Memo to: Dr. J. G. Bird

From: H. Stander

Subject: Analysis of Blood Pressure and Pulse Results from Subjects Given Placebo, Neo-Synephrine®, and Phenylpropanolamine, Orally.

As described in your memorandum of April 4, 1968, to Dr. Berberian from J. G. Bird, subject: Neo-Synephrine Cardiovascular Study, three doses of Neo-Synephrine (15, 20, and 25 mg), one dose of Phenylpropanolamine (50 mg), and a placebo were tested for their effect on pulse rate and blood pressure. Except for the set of treatmants, the experimental design was the same as that employed in the preceding study (see attached memorandum of January 5, 1967, to Dr. Luduena from H. Stander, subject: Analysis of Blood Pressure and Pulse Results from Subjects Given Placebo and Neo-Synephrine, Orally). The design consisted of four 5 x 5 latin squares; a total of 20 subjects received each of 5 medications over 5 test periods. All medications were randomly assigned to subjects and double-blind practices were followed throughout the study.

On each test period, each subject's blood pressure and pulse were taken on 7 occasions: 3 pre-medication (40 min., 20 min., 0 min.) and 4 post-medication (15 min., 30 min., 60 min., 120 min.). All readings are contained in the Appendix.

An analysis of the 3 pre-medication results showed no significant difference among the pulse rate readings, a significant decrease in systolic blood pressure from 40 min. to 20 min. to 0 min., and a significant difference between both 20 min. and 0 min. diastolic blood pressure readings and the 40 min. reading (see Table 1). Consequently, the average of the 3 pulse readings was assumed to provide a "best" estimate of each subject's pre-medication reading, and the 0 min. systolic and diastolic blood pressure readings were selected for the same reason.

The analysis of the relative or fractional changes in post-medication pulse showed significant differences between the placebo and two Neo-Synephrine® doses (15 mg and 25 mg) at the 30 min. observation time (see Table 2, Fig. 1); however the differences were not dose related.[A] This lack of a dose-response relationship may be due to the relatively small interval between consecutive doses and their probable position on the steep portion of the Neo-Synephrine dose-response curve (see (attached) January 5, 1967 report, fig. 1). If an average pre-medication reading of 80 beats/min. is assumed, at the 30 min. observation period the placebo reading would be equivalent to 76 beats/min. (0.955 x 80 beats/min.), and the

[A] To test the assumption that the specified dose of drug was given, excess capsules from each Neo-Synephrine dose were assayed by Analytical Chemistry and were found to contain doses of 15, 21, and 24 mg for noted doses of 15, 20, and 25 mg, respectively.

Neo-Synephrine 15 mg, 20 mg and 25 mg readings would be equivalent to 72, 75 and 73 beats/min., respectively. The response to Phenylpropanolamine (50 mg) was not significantly different from the response to placebo.

The post-medication relative systolic blood pressure readings showed a significant difference between Phenylpropanolamine (50 mg) and the placebo at the 60 min. and 120 min. observation times (see Table 3, fig. 2).

Relative diastolic blood pressure readings showed a significant difference between Neo Synephrine (15 mg) and the placebo at the 120 min. observation time (see Table 4, fig. 3).

H. Stander

Table 1

Pre-medication Readings from 20 subjects subsequently medicated with Placebo, Neo-Synephrine® (15 mg to 25 mg), and Phenylpropanolamine (50 mg), orally

Pre-medication time (min)	Parameter mean [a] Pulse (Beats/min)	Systolic B.P. (mm. Hg.)	Diastolic B (mm. Hg.)
40	76.8	115	71.3
20	76.2	113**	69.8**
0	76.3	112**	69.9**
Variance (152 d.f.)	14.1	12.9	12.3

[a] Each value represents a mean of 100 readings (20 subjects x 5 test periods for each subject).

** Significantly different from 40 minute reading, p = 0.01

Table 2

Fractional changes in Pulse readings from 20 Subjects medicated with Placebo, Neo-Synephrine® (15 mg to 25 mg), and Phenylpropanolamine (50 mg), orally

Medication	Time post-medication (min.) 15	30	60	12
Placebo	0.982	0.955	0.911	0.93
Neo-Synephrine®				
15 mg	0.952	0.906**	0.896	0.89
20 mg	0.975	0.934	0.892	0.89
25 mg	0.988	0.914*	0.890	0.89
Phenylpropanolamine				
50 mg	0.956	0.930	0.904	0.93
Variance (60 d.f.)	0.0034	0.0032	0.0034	0.03

* Significantly different from Placebo, p = 0.05

** Significantly different from Placebo, p = 0.01

Fig. 1 Fractional Changes in Pulse Readings from 20 Subjects Medicated with Placebo, Neo-Synephrine® (15 - 25 mg) and Phenylpropanolamine (50 mg), orally

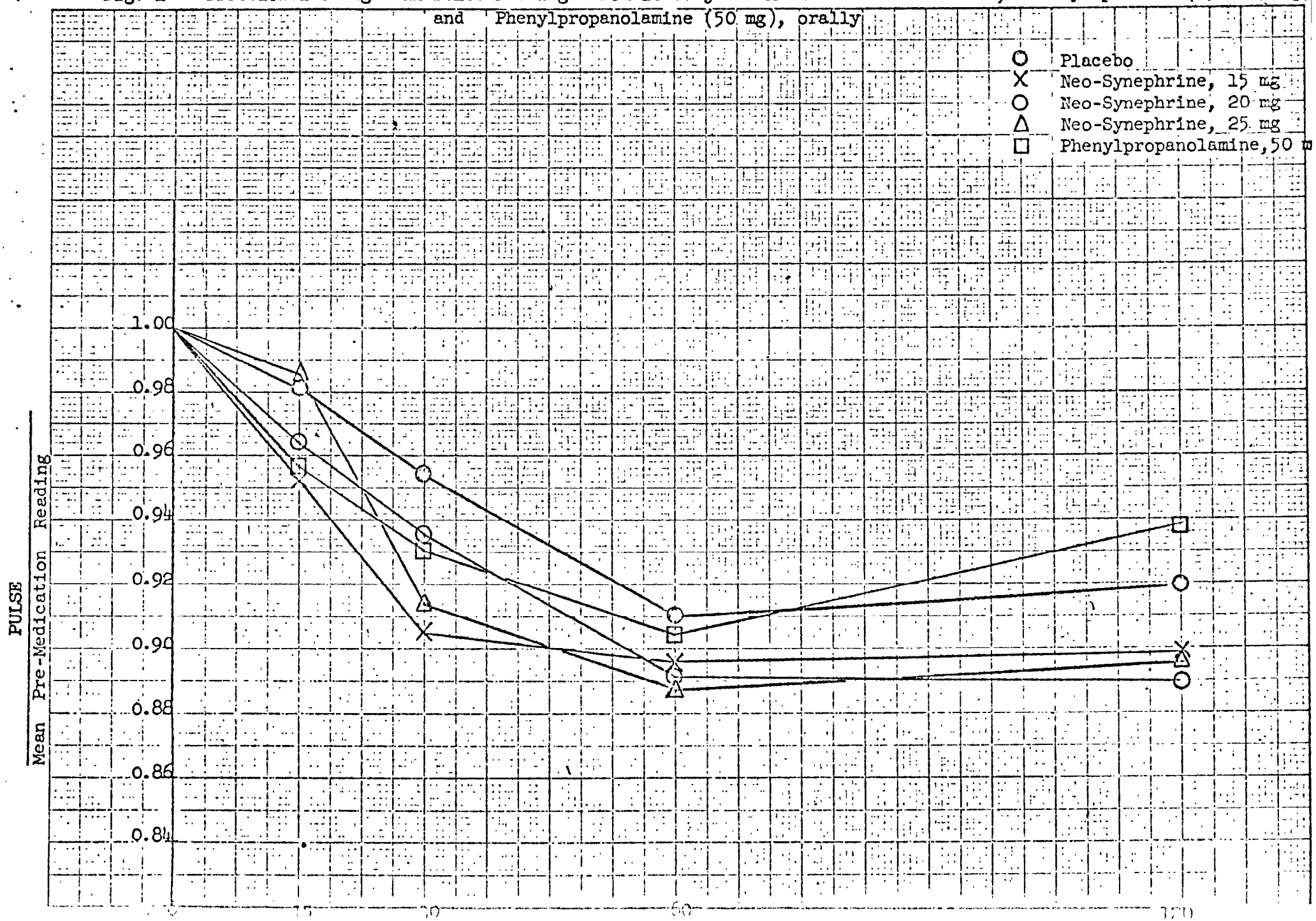


Table 3

Fractional Changes in Systolic Blood Pressure Readings from 20 Subjects Medicated with Placebo, Neo-Synephrine® (15 mg to 25 mg), and Phenylpropanolamine (50 mg), Orally

	Time post-medication, (min)			
Medication	15	30	60	120
Placebo	1.012	0.998	0.995	1.021
Neo-Synephrine®				
15 mg	0.993	0.986	0.982	0.992
20 mg	0.990	0.998	0.994	1.020
25 mg	1.009	0.996	1.008	1.018
Phenylpropanolamine				
50 mg	0.993	1.001	1.038**	1.068**
Variance (60 d.f.)	0.0019	0.0019	0.0026	0.0028

** Significantly different from Placebo, $p = 0.01$

Table 4

Fractional Changes in Diastolic Blood Pressure Readings from 20 Subjects Medicated with Placebo, Neo-Synephrine® (15 mg to 25 mg), and Phenylpropanolamine (50 mg), orally

	Time post-medication, (min)			
Medication	15	30	60	120
Placebo	1.032	1.059	1.065	1.082
Neo-Synephrine®				
15 mg	1.002	1.014	1.024	1.025*
20 mg	1.006	1.011	1.038	1.086
25 mg	1.026	1.030	1.032	1.048
Phenylpropanolamine				
50 mg	1.022	1.044	1.072	1.094
Variance (60 d.f.)	0.0052	0.0083	0.0068	0.0066

* Significantly different from Placebo, $p = 0.05$

Fig. 2 Fractional Changes in Systolic Blood Pressure Readings from 20 Subjects Medicated with Placebo, Neo-Synephrine® (15 - 25 mg), and Phenylpropanolamine (50 mg), orally

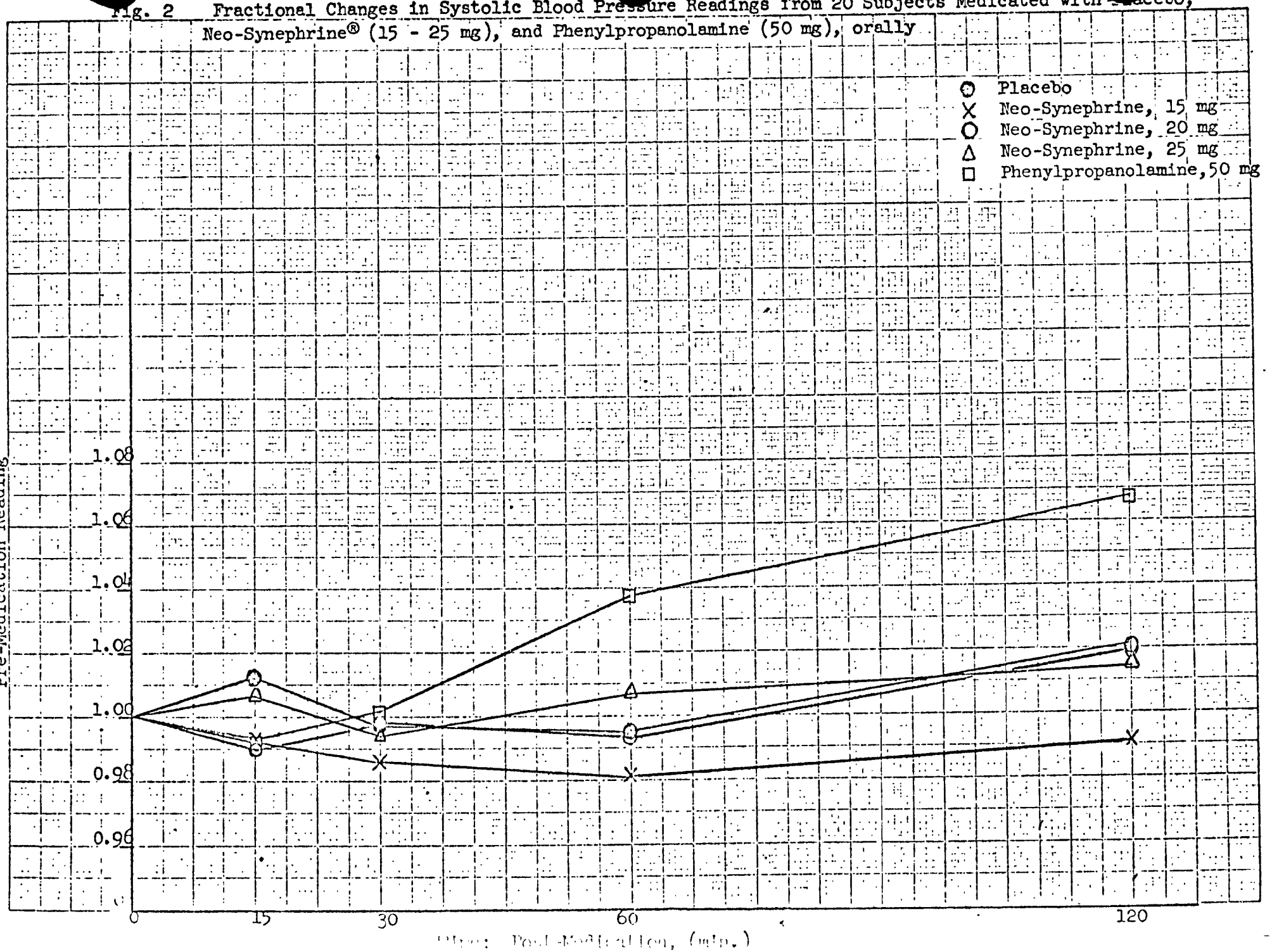
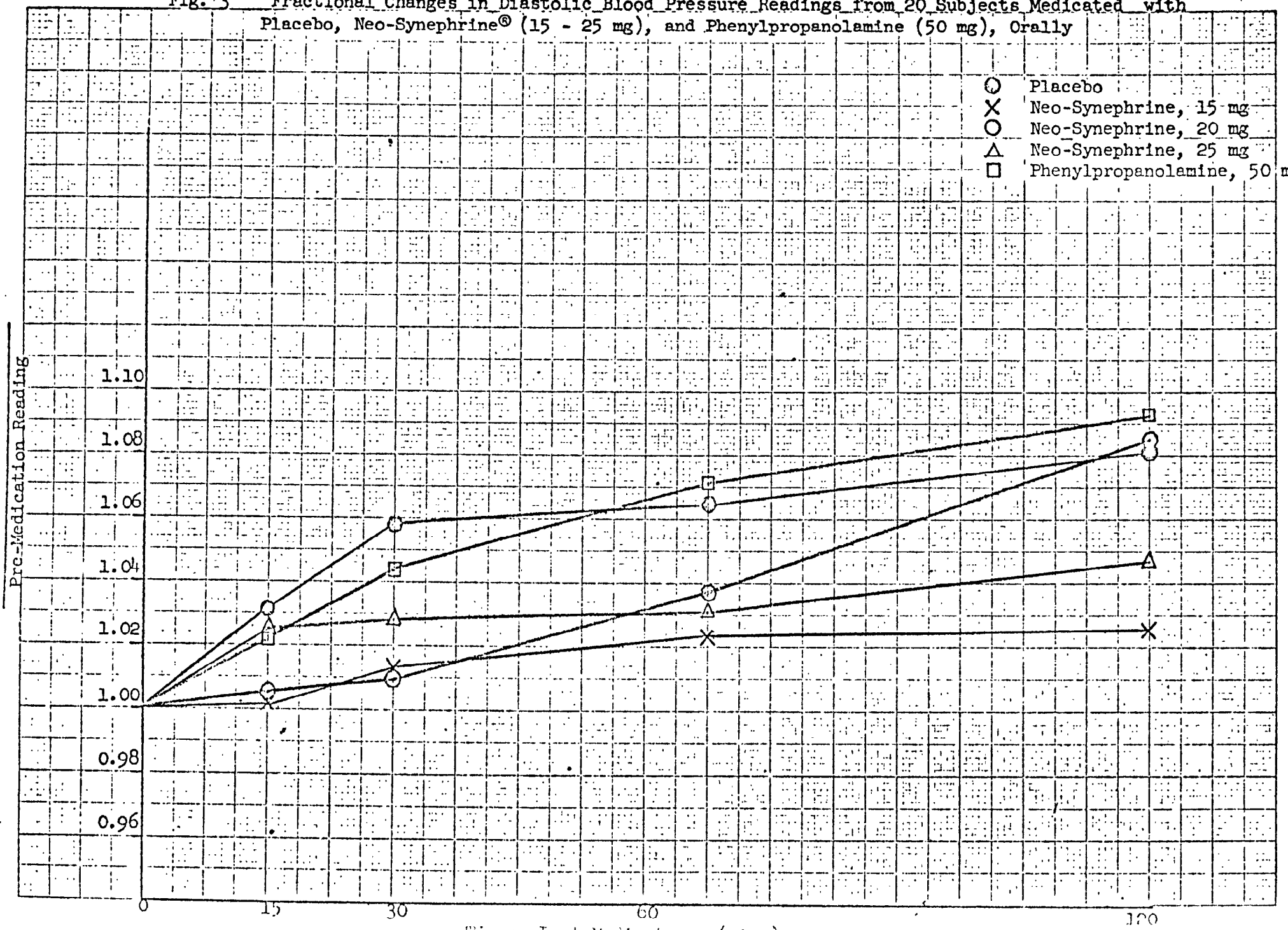


Fig. 3 Fractional Changes in Diastolic Blood Pressure Readings from 20 Subjects Medicated with Placebo, Neo-Synephrine® (15 - 25 mg), and Phenylpropanolamine (50 mg), Orally



APPENDIX

Table of Pulse Readings (B/min)

Subject	Medication Round	Medication Code	Pre-Medication 40 min	Pre-Medication 20 min	Pre-Medication 0 min	Post-Medication 15 min	Post-Medication 30 min	Post-Medication 60 min	Post-Medication 120 min
01	1	D	54	58	58	58	58	56	58
	2	B	58	62	60	56	58	58	60
	3	C	60	70	56	82	58	52	58
	4	E	64	62	60	60	52	52	60
	5	A	58	60	66	62	54	52	56
02	1	E	66	66	70	70	68	68	62
	2	D	70	68	64	68	64	62	60
	3	A	72	72	78	72	66	62	66
	4	C	60	68	68	68	62	58	60
	5	B	70	70	72	64	66	62	64
03	1	A	64	66	68	66	64	64	60
	2	C	56	64	64	58	56	56	58
	3	E	74	68	64	62	54	60	60
	4	B	58	60	60	58	60	58	60
	5	D	64	66	68	68	60	64	66
04	1	B	70	68	70	74	68	66	68
	2	E	66	66	74	68	66	64	62
	3	D	76	80	58	62	70	66	76
	4	A	72	76	68	70	68	64	72
	5	C	70	68	70	66	68	60	72
05	1	C	60	68	64	70	64	60	58
	2	A	66	62	62	68	62	58	58
	3	B	54	68	64	70	60	60	56
	4	D	66	62	62	62	62	60	58
	5	E	70	70	66	68	68	60	60
06	1	B	86	88	82	82	80	68	84
	2	E	78	74	78	76	74	70	72
	3	C	70	78	72	74	74	64	68
	4	D	86	86	92	86	82	80	86
	5	A	76	74	76	74	72	70	70
07	1	A	70	72	74	72	70	60	64
	2	C	80	72	74	68	64	70	66
	3	B	76	76	70	68	66	70	66
	4	E	74	78	76	64	68	74	64
	5	D	80	72	70	64	64	62	62
08	1	E	96	88	94	88	80	84	78
	2	D	108	102	98	96	98	88	86
	3	A	90	100	88	82	88	84	84
	4	C	88	88	88	84	78	86	72
	5	B	94	90	90	84	80	68	70

APPENDIX

Table of Pulse Readings (B/min)

Subject	Round	Medication Code	Pre-Medication 40 min	20 min	0 min	Post-Medication 15 min	30 min	60 min	120 min
09	1	C	80	80	80	84	80	78	82
	2	B	80	80	80	76	78	68	76
	3	D	96	94	96	90	94	96	100
	4	A	92	92	90	92	88	86	82
	5	E	84	76	84	82	80	76	80
10	1	D	84	84	84	82	84	72	80
	2	A	88	86	84	84	80	84	72
	3	E	90	90	96	84	76	82	76
	4	B	90	88	88	78	88	74	84
	5	C	88	90	90	80	80	88	68
11	1	E	92	84	88	88	88	88	80
	2	C	86	86	92	96	90	88	84
	3	B	90	86	92	90	90	88	86
	4	D	82	86	90	88	88	84	88
	5	A	88	90	88	90	88	80	80
12	1	C	76	74	78	74	66	64	62
	2	B	66	70	72	72	70	66	60
	3	D	72	72	80	66	68	62	60
	4	A	72	70	76	72	68	62	64
	5	E	70	64	66	66	60	50	56
13	1	B	68	70	68	74	72	64	64
	2	A	66	64	62	60	62	56	54
	3	C	70	62	66	62	56	58	58
	4	E	68	66	64	64	58	58	68
	5	D	66	74	70	66	62	62	66
14	1	A	94	90	94	90	88	86	88
	2	D	88	86	96	90	80	84	88
	3	E	90	88	92	86	84	84	88
	4	C	90	94	88	90	84	68	90
	5	B	96	88	90	92	84	88	84
15	1	D	70	68	70	68	64	64	68
	2	E	68	70	70	72	76	62	68
	3	A	76	64	78	68	74	66	72
	4	B	74	70	76	76	76	74	72
	5	C	74	74	72	70	68	68	64
16	1	A	80	80	76	76	76	72	72
	2	E	88	86	84	80	78	74	72
	3	D	70	68	80	68	60	60	78
	4	C	74	76	72	78	66	70	72
	5	B	74	72	74	74	64	66	66

APPENDIX

Table of Pulse Readings (B/min)

Subject	Round	Medication Code	Pre-Medication 40 min	20 min	0 min	Post-Medication 15 min	30 min	60 min	120 min
17	1	D	66	72	64	62	62	54	58
	2	A	80	70	66	68	62	60	60
	3	B	74	70	74	74	66	66	66
	4	E	76	78	76	72	72	68	74
	5	C	76	68	70	68	70	62	66
18	1	C	90	88	88	74	78	78	72
	2	D	94	88	88	80	66	78	80
	3	E	90	84	80	78	76	74	76
	4	B	74	84	88	84	80	80	80
	5	A	100	90	84	92	80	74	80
19	1	B	66	64	58	62	62	58	56
	2	C	66	62	62	60	54	60	60
	3	A	64	60	60	58	52	54	54
	4	D	60	64	68	66	66	64	60
	5	E	72	68	68	60	60	64	60
20	1	E	84	86	82	80	58	72	68
	2	B	84	88	88	80	78	74	68
	3	C	100	94	92	90	72	68	72
	4	A	100	102	98	98	92	100	74
	5	D	84	82	80	80	80	76	68

A = 20 mg Neo-Synephrine

B = Placebo

C = 25 mg Neo-Synephrine

D = 50 mg Phenylpropanolamine

E = 15 mg Neo-Synephrine

Table of Systolic Blood Pressure Readings (mm Hg)

Subject	Medication Round	Medication Code	Pre-Medication 40 min	Pre-Medication 20 min	Pre-Medication 0 min	Post-Medication 15 min	Post-Medication 30 min	Post-Medication 60 min	Post-Medication 120 min
01	1	D	124	112	110	110	110	120	122
	2	B	118	116	112	120	120	112	116
	3	C	110	108	106	120	108	110	114
	4	E	130	110	112	112	110	112	112
	5	A	106	110	112	104	100	108	106
02	1	E	110	102	102	100	102	104	102
	2	D	112	110	110	104	110	118	120
	3	A	112	116	104	104	108	110	110
	4	C	110	110	104	104	104	116	112
	5	B	116	108	112	100	110	116	110
03	1	A	116	110	110	110	112	118	116
	2	C	120	110	114	110	110	114	112
	3	E	112	106	100	102	110	108	112
	4	B	116	110	116	108	110	110	116
	5	D	114	110	116	110	112	116	126
04	1	B	120	110	110	112	104	110	110
	2	E	106	104	106	112	100	110	106
	3	D	114	110	110	104	104	102	104
	4	A	112	112	108	102	110	100	104
	5	C	126	118	110	110	110	114	116
05	1	C	104	100	100	104	102	102	96
	2	A	116	114	114	116	110	116	116
	3	B	108	108	112	110	110	112	110
	4	D	120	112	110	108	112	116	110
	5	E	108	112	116	114	106	110	110
06	1	B	130	124	120	128	116	120	120
	2	E	124	124	120	124	128	124	122
	3	C	116	116	118	114	118	120	122
	4	D	120	116	120	120	126	128	130
	5	A	124	124	116	126	124	116	124
07	1	A	106	106	102	102	102	104	104
	2	C	114	116	106	110	110	108	110
	3	B	108	108	102	100	108	100	104
	4	E	108	100	106	104	108	104	110
	5	D	110	108	108	104	120	130	126
08	1	E	110	112	110	110	110	106	104
	2	D	118	112	112	106	114	110	112
	3	A	100	108	100	96	100	100	104
	4	C	114	114	108	110	106	100	108
	5	B	114	112	100	100	100	102	102

Table of Systolic Blood Pressure Readings (mm Hg)

Subject	Round	Med. Code	Pre-Medication 40 min	20 min	0 min	Post-Medication 15 min	30 min	60 min	120 min
[illegible]09	1	C	142	142	140	138	138	140	142
	2	B	136	134	130	130	130	128	130
	3	D	140	146	144	144	152	144	140
	4	A	130	130	134	132	140	130	136
	5	E	144	130	130	130	134	136	130
10	1	D	130	128	128	122	124	122	126
	2	A	124	130	130	124	124	130	132
	3	E	126	126	128	120	126	122	126
	4	B	126	134	130	136	126	130	134
	5	C	136	126	130	130	126	126	124
11	1	E	120	110	112	110	108	108	110
	2	C	112	112	110	120	108	108	106
	3	B	116	110	110	110	106	116	110
	4	D	106	106	106	106	106	112	130
	5	A	116	110	110	110	108	104	110
12	1	C	112	112	118	110	110	116	118
	2	B	108	114	110	110	110	110	114
	3	D	104	106	110	110	114	120	108
	4	A	110	110	106	110	106	110	110
	5	E	114	110	110	112	110	108	104
[illegible]13	1	B	106	108	110	112	112	102	110
	2	A	104	110	112	112	108	114	114
	3	C	110	110	108	110	116	110	116
	4	E	102	110	118	112	112	112	120
	5	D	116	116	120	122	118	116	122
14	1	A	120	118	116	120	116	112	118
	2	D	124	118	118	122	112	120	126
	3	E	120	118	116	116	116	108	120
	4	C	120	108	112	108	106	106	116
	5	B	110	112	112	116	118	112	130
15	1	D	130	124	118	130	120	118	130
	2	E	120	120	118	118	120	120	120
	3	A	126	126	118	114	126	118	116
	4	B	126	122	120	130	116	112	126
	5	C	122	120	120	114	120	120	120
16	1	A	124	124	122	118	118	116	124
	2	E	124	124	126	126	124	124	130
	3	D	120	118	114	112	118	130	144
	4	C	124	130	124	120	120	110	124
	5	B	110	110	106	116	116	110	116

Table of Systolic Blood Pressure Readings (mm Hg)

Subject	Round	Med. Code	Pre-Medication 40 min	Pre-Medication 20 min	Pre-Medication 0 min	Post-Medication 15 min	Post-Medication 30 min	Post-Medication 60 min	Post-Medication 120 min
17	1	D	110	110	110	106	96	100	110
	2	A	112	106	104	96	100	96	96
	3	B	110	98	100	100	100	104	100
	4	E	110	110	106	104	102	106	100
	5	C	104	98	98	96	96	102	96
18	1	C	100	104	90	90	94	96	90
	2	D	96	96	96	94	98	104	104
	3	E	100	100	96	90	88	88	90
	4	B	100	96	96	92	90	90	92
	5	A	96	96	96	90	90	96	96
19	1	B	106	110	110	112	108	108	110
	2	C	100	110	100	110	106	106	106
	3	A	108	104	96	100	102	100	116
	4	D	104	100	106	112	106	112	112
	5	E	104	102	110	106	104	100	100
20	1	E	110	112	108	112	104	102	106
	2	B	106	100	98	102	102	100	104
	3	C	106	104	104	108	100	106	110
	4	A	120	110	100	102	102	100	100
	5	D	100	104	100	106	102	110	114

A = 20 mg Neo-Synephrine

B = Placebo

C = 25 mg Neo-Synephrine

D = 50 mg Phenylpropanolamine

E = 15 mg Neo-Synephrine

Table of Diastolic Blood Pressure Readings (mm Hg)

Subject	Medication Round	Medication Code	Pre-Medication 40 min	Pre-Medication 20 min	Pre-Medication 0 min	Post-Medication 15 min	Post-Medication 30 min	Post-Medication 60 min	Post-Medication 120 min
01	1	D	64	58	60	60	62	64	70
	2	B	60	60	60	64	70	64	62
	3	C	50	64	64	70	68	66	80
	4	E	80	60	70	70	60	70	72
	5	A	58	64	60	60	60	60	68
02	1	E	80	74	70	80	74	74	72
	2	D	74	74	70	70	78	80	80
	3	A	80	76	70	76	72	80	80
	4	C	76	80	70	80	80	80	80
	5	B	76	76	70	70	70	76	80
03	1	A	70	66	64	60	72	70	70
	2	C	80	60	60	70	74	78	74
	3	E	72	60	60	70	70	58	70
	4	B	72	60	74	70	70	72	70
	5	D	78	76	76	70	72	76	80
04	1	B	70	72	70	70	74	70	80
	2	E	70	68	68	68	68	74	60
	3	D	60	62	60	70	74	72	74
	4	A	62	62	68	66	70	62	70
	5	C	70	70	68	72	70	68	78
05	1	C	64	60	60	64	60	60	70
	2	A	62	60	60	62	60	62	62
	3	B	58	60	50	58	56	60	58
	4	D	70	70	62	64	72	62	66
	5	E	64	58	60	66	68	64	60
06	1	B	86	80	80	80	80	80	80
	2	E	84	80	80	80	80	90	90
	3	C	80	78	80	80	90	80	84
	4	D	78	76	80	82	84	90	90
	5	A	80	80	80	84	86	80	84
07	1	A	76	68	60	62	60	70	74
	2	C	70	64	60	70	70	68	70
	3	B	64	64	62	70	70	62	80
	4	E	64	64	66	64	68	70	70
	5	D	62	62	68	70	64	80	80
08	1	E	68	70	70	70	70	70	70
	2	D	70	68	70	68	70	70	70
	3	A	60	66	66	60	60	60	82
	4	C	64	60	66	60	66	64	68
	5	B	64	64	60	64	64	70	70

Table of Diastolic Blood Pressure Readings (mm Hg)

Subject	Round	Medication Code	Pre-Medication 40 min	Pre-Medication 20 min	Pre-Medication 0 min	Post-Medication 15 min	Post-Medication 30 min	Post-Medication 60 min	Post-Medication 120 min
09	1	C	90	92	96	100	100	100	100
	2	B	96	90	90	94	94	90	94
	3	D	100	100	100	102	104	104	104
	4	A	90	90	90	92	94	94	96
	5	E	94	90	94	90	100	100	100
10	1	D	88	88	88	80	84	90	90
	2	A	90	90	94	90	90	96	100
	3	E	90	90	88	84	88	90	98
	4	B	84	90	90	90	88	92	90
	5	C	90	90	88	90	86	90	90
11	1	E	70	70	74	68	68	70	72
	2	C	70	66	68	74	70	70	68
	3	B	72	72	70	70	72	72	80
	4	D	76	70	76	80	76	76	78
	5	A	72	72	72	76	74	74	80
12	1	C	70	70	76	74	70	76	78
	2	B	70	70	70	70	70	72	70
	3	D	76	72	72	72	76	80	70
	4	A	70	68	68	70	70	76	70
	5	E	72	70	70	64	70	70	70
13	1	B	70	64	68	68	68	70	70
	2	A	64	62	60	58	58	74	80
	3	C	62	60	58	58	62	62	62
	4	E	60	68	58	60	68	68	68
	5	D	62	66	72	78	70	68	80
14	1	A	76	76	74	74	70	70	70
	2	B	72	70	70	70	70	80	80
	3	E	66	66	66	72	72	70	70
	4	C	70	60	70	62	62	68	66
	5	B	70	70	66	70	70	76	80
15	1	D	84	84	72	84	84	80	84
	2	E	80	78	78	90	86	80	80
	3	A	80	86	82	82	90	90	86
	4	B	80	80	82	82	80	84	90
	5	C	78	80	80	80	84	88	76
16	1	A	78	80	78	64	64	76	80
	2	E	80	68	80	76	78	80	80
	3	D	80	72	70	74	88	90	80
	4	C	84	80	78	70	72	70	76
	5	B	70	70	70	72	74	78	70

Table of Diastolic Blood Pressure Readings (mm Hg)

		Medication	Pre-Medication			Post-Medication			
Subject	Round	Code	40 min	20 min	0 min	15 min	30 min	60 min	120 min
17	1	D	64	64	60	60	60	66	60
	2	A	70	66	60	60	60	60	62
	3	B	62	60	58	60	68	70	70
	4	E	66	70	72	64	62	70	70
	5	C	60	60	60	64	60	60	60
18	1	C	58	60	70	70	70	70	60
	2	D	60	66	66	70	70	60	70
	3	E	70	66	66	58	58	60	60
	4	B	60	60	56	60	60	60	60
	5	A	52	54	62	70	66	66	64
19	1	B	60	60	62	62	62	60	60
	2	C	60	60	68	60	60	60	60
	3	A	62	62	62	62	60	60	60
	4	D	70	70	66	64	66	74	70
	5	E	60	54	64	62	60	62	60
20	1	E	62	62	62	60	64	62	62
	2	B	58	60	60	62	78	70	60
	3	C	60	60	60	64	64	64	60
	4	A	74	58	60	68	68	62	68
	5	D	58	60	62	60	56	60	74

A = 20 mg Neo-Synephrine

B = Placebo

C = 25 mg Neo-Synephrine

D = 50 mg Phenylpropanolamine

E = 15 mg Neo-Synephrine

REFERENCE 23

INTEROFFICE MEMORANDUM

STERLING-WINTHROP RESEARCH INSTITUTE

RENSSELAER, NEW YORK

January 5, 1967

Ref 3

Memo to: Dr. Luduena

From: H. Stander

Subject: EP 14. Analysis of Blood Pressure and Pulse Results from Subjects given Placebo and Neo-Synephrine®, Orally.

As described in an interoffice memorandum; October 18, 1966, to Dr. Suter from F. P. Luduena, subject: Testing of Neo-Synephrine® Orally on Volunteers, a placebo and four doses of Neo-Synephrine® (10, 25, 50 and 100 mg) were tested for their effect on pulse rate and blood pressure. The statistical design consisted of four 5 x 5 x 5 latin squares; a total of 20 subjects received each of 5 medications over 5 test periods. All medications were randomly assigned to subjects and double-blind practices were followed throughout the study.

On each test period, each subject's blood pressure and pulse was taken on 7 occasions; 3 pre-medication (40 min., 20 min., 0 min.) and 4 post-medication (15 min., 30 min., 60 min., 120 min.). All readings are contained on the Appendix.

An analysis of the 3 pre-medication readings for each parameter showed no significant differences between the 20 min. and 0 min. means; however, there were significant differences between these means and the 40 min. results (see table 1). Consequently, the 40 min. readings were not employed in the calculation of the relative post-medication results.

The analysis of the relative or fractional changes in post-medication pulse showed maximum dose-related differences between the placebo and Neo-Synephrine® medications at the 60 min. observation time (see fig. 1 and table 2). Neo-Synephrine® 25 mg, 50 mg, and 100 mg elicited responses which were significantly less than the response to placebo; if an average pre-medication reading of 80 beats/min. is assumed, at the 60 min. observation period the placebo reading would be equivalent to 75 beats/min. (0.939 x 80 beats/min.), and the Neo-Synephrine 25 mg, 50 mg, and 100 mg readings would be equivalent to 71, 70, and 68 beats/min., respectively.

The post-medication systolic blood pressure readings showed a significant difference between Neo-Synephrine @ 100 mg and the placebo at the 30 min. and 60 min. observation times (see fig. 2 and table 3).

There were no significant differences between medications with respect to diastolic blood pressure (see fig. 3 and table 4).

In no case did Neo-Synephrine @ 10 mg elicit a response significantly different from the response to placebo.

H. Stander

HS/jd

cc: Dr. Albertson
Dr. Archer
Dr. Bell
Dr. Clinton
Dr. Gorman
Dr. Lands
Mr. Mingo
Dr. Surrey
Dr. Suter
Dr. Tullar
Dr. Wessinger
Dr. Zenitz
file

Table 1

Pre-Medication Readings from 20 Subjects Subsequently Medicated with Placebo and Neo-Synephrine ® (10 mg to 100 mg), orally

Parameter Mean [A]			
Pre-medication time, (min.)	Pulse (Beats/min.)	Systolic B.P. (mm. Hg)	Diastolic B.P. (mm. Hg)
40	81.3	117	72.4
20	79.8*	114**	71.1*
0	80.4	113**	71.2*
Variance (152 d.f.)	18.2	18.9	14.4

[A] Each value represents a mean of 100 readings (20 subjects x 5 test periods for each subject).

* significantly different from 40 minute reading, p = 0.05

** significantly different from 40 minute reading, p = 0.01

Fig. Fractional Changes in Pulse Readings from 20 Subjects Treated with Placebo and Neosynephrine® (10–100 mg), Orally.

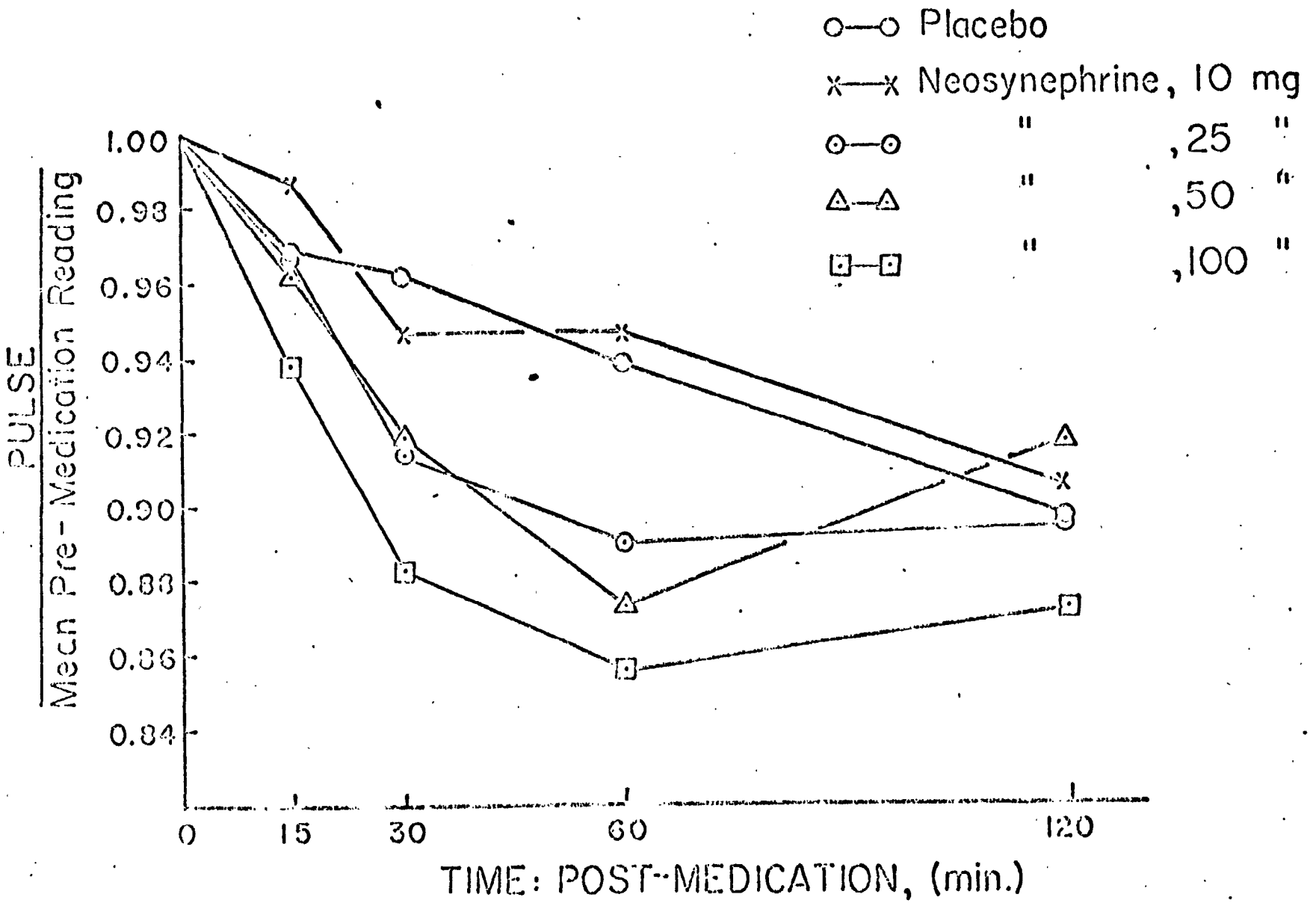


Table 2

Fractional Changes in Pulse Readings from 20 Subjects Medicated with Placebo and Neo-Synephrine® (10 mg to 100 mg), orally

Neo-Synephrine® Dose	Time post-medication, (min.)* 15	30	60	120
0 mg (Placebo)	0.968	0.962	0.939	0.897
10 mg	0.987	0.946	0.946	0.906
25 mg	0.968	0.914	0.890*	0.896
50 mg	0.962	0.918	0.874**	0.919
100 mg	0.938	0.882*	0.856**	0.872
Variance (60 d.f.)	0.0052	.0073	0.0050	0.0058

* significantly different from 0 mg (Placebo), p = 0.05

** significantly different from 0 mg (Placebo), p = 0.01

Fig. 2 Fractional Changes in Systolic Blood Pressure Readings from 20 Subjects Medicated with Placebo and Neosynephrine® (10–100 mg), Orally.

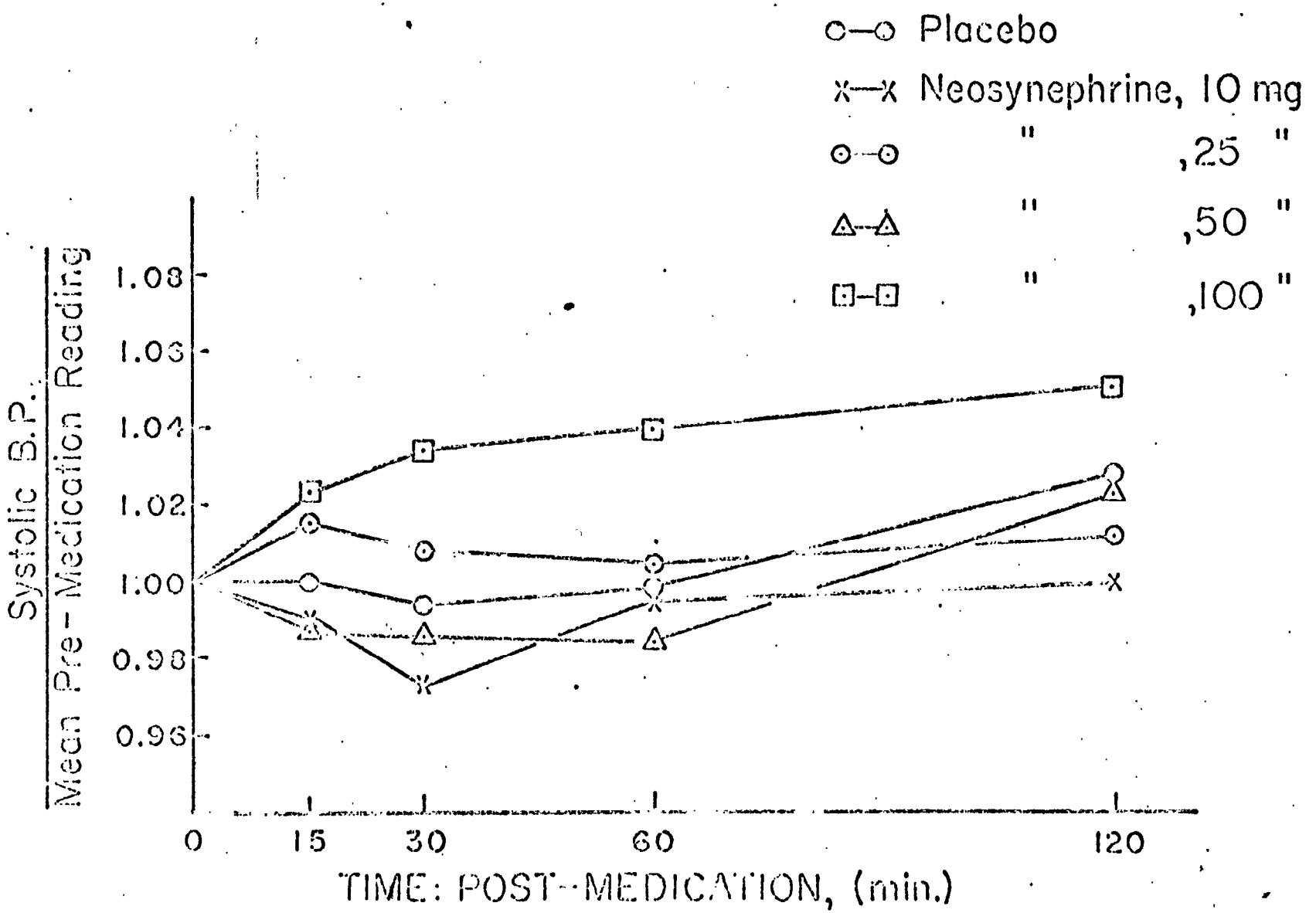


Table 3

Fractional Changes in Systolic Blood Pressure Readings from 20 Subjects Medicated with Placebo and Neo-Synephrine® (10 mg to 100 mg), orally

Neo-Synephrine® Dose	Time post-medication, (min.) 15	30	60	120
0 mg (Placebo)	1.000	0.994	0.998	1.027
10 mg	0.990	0.974	0.996	0.999
25 mg	1.016	1.008	1.004	1.010
50 mg	0.988	0.986	0.984	1.022
100 mg	1.023	1.034*	1.039*	1.050
Variance (60 d.f.)	0.0033	0.0026	0.0027	0.0025

* Significantly different from 0 mg (Placebo), $p = 0.05$.

Fig. 3 Fractional Changes in Diastolic Blood Pressure Readings from 20 Subjects Medicated with Placebo and Neosynephrine® (10 -- 100 mg), Orally.

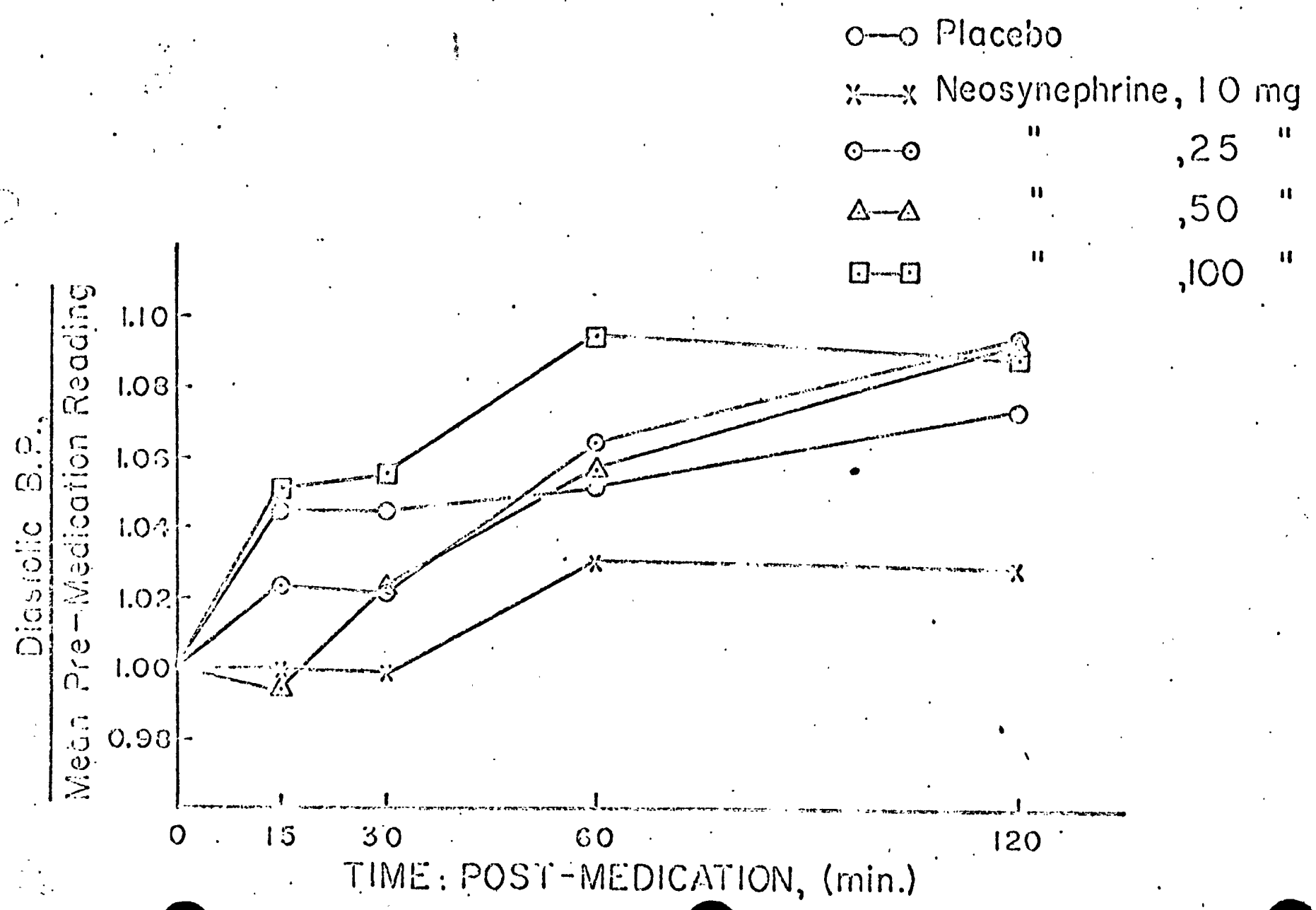


Table 4

Fractional Changes in Diastolic Blood Pressure Readings from 20 Subjects Medicated with Placebo and Neo-Synephrine® (10 mg to 100 mg), orally

Neo-Synephrine® Dose	Time post-medication, (min.) 15	30	60	120
0 mg (Placebo)	1.046	1.044	1.051	1.074
10 mg	1.000	1.000	1.031	1.030
25 mg	1.024	1.022	1.057	1.093
50 mg	0.996	1.022	1.057	1.093
100 mg	1.052	1.056	1.094	1.090
Variance (60 d.f.)	0.0061	0.0078	0.0100	0.0103

APPENDIX

Table of Pulse Readings (B/min.)

Subject	Round	Medication Code	Pre medication 40 min	20 min	0 min	Post Medication 15 min	20 min	60 min	120 min
01	1	D	64	68	72	70	68	56	56
	2	B	62	66	64	70	76	70	60
	3	C	68	66	70	66	68	54	60
	4	E	66	72	76	64	64	64	56
	5	A	74	76	76	72	72	76	64
02	1	E	76	78	80	70	70	68	64
	2	D	84	78	76	76	78	64	66
	3	A	84	68	78	78	64	74	78
	4	C	70	80	76	70	68	72	76
	5	B	80	80	76	70	80	82	70
03	1	A	72	64	68	68	70	62	66
	2	C	70	76	76	76	66	66	66
	3	E	70	70	74	70	70	68	68
	4	B	76	72	74	74	66	72	66
	5	D	86	78	74	74	74	66	68
04	1	B	86	96	96	88	80	80	82
	2	E	100	108	100	88	78	80	82
	3	D	94	88	96	96	76	84	80
	4	A	100	92	84	82	86	80	80
	5	C	86	88	94	94	86	92	84
05	1	C	74	70	76	68	68	62	64
	2	A	78	80	82	74	76	72	70
	3	B	70	76	84	76	68	68	70
	4	D	72	80	74	72	68	66	68
	5	E	76	74	82	84	80	72	66
06	1	B	72	64	68	84	84	80	88
	2	E	88	80	88	72	62	78	74
	3	C	96	88	90	88	86	84	82
	4	D	112	98	100	94	94	90	100
	5	A	94	94	86	88	94	88	84
07	1	A	64	66	68	62	58	60	68
	2	C	72	68	74	72	62	58	68
	3	B	82	58	74	70	70	64	62
	4	E	70	70	82	78	64	58	60
	5	D	88	80	78	76	60	82	74
08	1	E	86	88	88	82	68	56	70
	2	D	72	78	72	72	74	60	68
	3	A	94	90	82	82	78	82	68
	4	C	76	78	76	72	66	66	66
	5	B	80	64	78	74	66	76	62

APPENDIX

Table of Pulse Readings (B/min.)

Subject	Round	Medication Code	Pre medication 40 min	20 min	0 min	Post Medication 15 min	20 min	60 min	120 min
01	1	D	64	68	72	70	68	56	56
	2	B	62	66	64	70	76	70	60
	3	C	68	66	70	66	68	54	60
	4	E	66	72	76	64	64	64	56
	5	A	74	76	76	72	72	76	64
02	1	E	76	78	80	70	70	68	64
	2	D	84	78	76	76	78	64	66
	3	A	84	68	78	78	64	74	78
	4	C	70	80	76	70	68	72	76
	5	B	80	80	76	70	80	82	70
03	1	A	72	64	68	68	70	62	66
	2	C	70	76	76	76	66	66	66
	3	E	70	70	74	70	70	68	68
	4	B	76	72	74	74	66	72	66
	5	D	86	78	74	74	74	66	68
04	1	B	86	96	96	88	80	80	82
	2	E	100	108	100	88	78	80	82
	3	D	94	88	96	96	76	84	80
	4	A	100	92	84	82	86	80	80
	5	C	86	88	94	94	86	92	84
05	1	C	74	70	76	68	68	62	64
	2	A	78	80	82	74	76	72	70
	3	B	70	76	84	76	68	68	70
	4	D	72	80	74	72	68	66	68
	5	E	76	74	82	84	80	72	66
06	1	B	72	64	68	84	84	80	88
	2	E	88	80	88	72	62	78	74
	3	C	96	88	90	88	86	84	82
	4	D	112	98	100	94	94	90	100
	5	A	94	94	86	88	94	88	84
07	1	A	64	66	68	62	58	60	68
	2	C	72	68	74	72	62	58	68
	3	B	82	58	74	70	70	64	62
	4	E	70	70	82	78	64	58	60
	5	D	88	80	78	76	60	82	74
08	1	E	86	88	88	82	68	56	70
	2	D	72	78	72	72	74	60	68
	3	A	94	90	82	82	78	82	68
	4	C	76	78	76	72	66	66	66
	5	B	80	64	78	74	66	76	62

Table of Pulse Readings (B/min.) (cont'd.)

Subject	Round	Medication Code	Pre medication 40 min	20 min	0 min	Post medication 15 min	20 min	60 min	120 min
09	1	C	72	74	74	70	68	68	64
	2	B	70	76	76	72	70	68	68
	3	D	80	74	72	74	70	64	72
	4	A	80	78	80	80	76	70	72
	5	E	84	82	86	68	66	76	70
10	1	D	96	96	88	78	84	82	86
	2	A	100	98	88	96	88	84	90
	3	E	98	100	100	96	90	82	80
	4	B	100	100	92	96	88	90	82
	5	C	96	94	88	84	84	86	82
11	1	E	60	56	66	64	66	60	56
	2	C	70	70	68	68	58	62	58
	3	B	56	66	62	60	54	64	58
	4	D	68	62	64	60	60	54	64
	5	A	66	60	64	62	56	56	54
12	1	C	100	86	80	76	76	72	68
	2	B	74	72	76	72	74	64	68
	3	D	80	82	84	76	70	70	74
	4	A	82	80	82	74	78	74	70
	5	E	96	90	86	78	84	80	70
13	1	B	76	80	82	76	62	74	70
	2	A	90	84	82	82	86	84	74
	3	C	80	82	80	78	74	72	70
	4	E	72	72	78	76	72	68	74
	5	D	80	76	76	74	70	64	76
14	1	A	78	86	84	88	88	82	78
	2	D	86	90	88	84	82	78	90
	3	E	78	74	62	68	64	64	68
	4	C	70	78	80	80	66	76	72
	5	B	76	76	82	76	74	74	68
15	1	D	68	64	78	70	68	62	60
	2	E	60	60	64	62	50	52	60
	3	A	60	62	70	62	62	64	60
	4	B	62	70	66	68	64	62	56
	5	C	66	66	68	66	66	62	66
16	1	A	100	96	100	74	94	88	70
	2	E	86	90	84	92	82	78	88
	3	D	96	92	94	84	78	84	84
	4	C	104	98	96	92	92	90	86
	5	B	110	104	94	88	84	78	90

Table of Pulse Readings (B/min.) (cont'd.)

Subject	Round	Medication Code	Pre medication 40 min	20 min	0 min	Post medication 15 min	20 min	60 min	120 min
17	1	D	86	86	82	88	78	72	74
	2	A	96	96	94	90	90	82	76
	3	B	96	94	90	92	84	84	74
	4	E	86	84	78	62	68	66	70
	5	C	96	86	90	82	80	74	74
18	1	C	74	72	72	72	70	64	76
	2	D	74	74	78	74	70	76	74
	3	E	74	74	80	72	72	62	78
	4	B	72	74	74	70	70	74	78
	5	A	74	70	76	74	72	70	68
19	1	B	76	80	70	68	66	60	56
	2	C	100	84	72	78	62	60	60
	3	A	92	82	74	76	74	64	60
	4	D	68	66	72	60	60	50	56
	5	E	68	64	66	58	54	54	54
20	1	E	100	104	100	100	90	88	88
	2	B	96	96	100	98	94	90	90
	3	C	104	102	96	96	98	88	90
	4	A	92	88	90	88	86	100	88
	5	D	100	100	106	104	100	94	100

Medication Code

A = Placebo
B = 10 mg. Neo-Synephrine ⊖
C = 25 mg. Neo-Synephrine ⊖
D = 50 mg. Neo-Synephrine ⊖
E = 100 mg. Neo-Synephrine ⊖

Table of Systolic Blood Pressure Readings (mm.Hg)

Subject	Round	Medication Code	Pre medication 40 min	20 min	0 min	Post medication 15 min	20 min	60 min	120 min
01	1	D	118	110	108	100	104	108	112
	2	B	110	100	100	96	100	100	100
	3	C	116	110	100	110	102	108	110
	4	E	120	100	104	100	102	102	112
	5	A	106	102	102	106	102	106	106
02	1	E	116	108	110	114	114	108	112
	2	D	108	108	106	114	108	106	100
	3	A	100	108	108	100	100	104	100
	4	C	108	104	104	116	110	106	110
	5	B	118	110	108	108	108	110	100
03	1	A	122	118	118	114	112	106	110
	2	C	120	118	110	110	120	114	108
	3	E	116	116	110	112	116	122	116
	4	B	130	124	126	110	110	112	116
	5	D	132	120	112	122	112	114	128
04	1	B	114	114	114	100	104	110	110
	2	E	110	100	100	110	100	100	108
	3	D	120	108	102	112	104	90	104
	4	A	104	106	100	100	96	100	116
	5	C	108	106	106	106	102	102	102
05	1	C	112	106	108	110	114	112	110
	2	A	108	110	100	110	110	108	102
	3	B	120	108	102	108	110	112	102
	4	D	100	104	100	100	104	106	112
	5	E	110	110	110	110	106	110	116
06	1	B	134	130	134	134	130	128	130
	2	E	120	116	120	112	130	130	124
	3	C	128	124	118	120	134	130	128
	4	D	126	138	130	140	134	134	128
	5	A	138	136	136	140	136	132	140
07	1	A	136	116	114	114	116	120	120
	2	C	118	114	122	112	122	120	122
	3	B	122	120	130	136	124	126	132
	4	E	122	120	122	122	132	128	130
	5	D	130	134	130	120	130	122	140
08	1	E	116	112	110	118	118	122	120
	2	D	118	118	110	112	112	112	110
	3	A	124	116	120	116	112	124	120
	4	C	120	112	126	126	116	120	118
	5	B	110	116	108	114	110	120	120

Table of Systolic Blood Pressure Readings (mm.Hg) (cont'd.)

Subject	Round	Medication Code	Pre medication 40 min	20 min	0 min	Post medication 15 min	20 min	60 min	120 min
09	1	C	110	116	116	110	112	108	120
	2	B	112	110	110	122	110	116	130
	3	D	124	120	120	118	118	120	130
	4	A	122	116	120	112	124	120	110
	5	E	110	110	112	122	114	120	120
10	1	D	130	120	120	102	106	110	114
	2	A	122	122	112	122	120	120	122
	3	E	118	124	130	124	128	120	120
	4	B	126	110	112	114	112	116	110
	5	C	122	120	120	114	114	110	120
11	1	E	120	110	110	114	112	108	120
	2	C	132	130	120	120	116	128	116
	3	B	108	110	110	110	106	120	108
	4	D	112	112	112	112	108	110	110
	5	A	110	108	110	104	110	110	114
12	1	C	130	120	130	124	108	114	120
	2	B	120	120	116	110	112	108	112
	3	D	110	110	110	114	110	108	110
	4	A	118	108	110	110	110	110	108
	5	E	126	120	116	116	116	118	114
13	1	B	124	130	126	120	124	128	130
	2	A	124	120	122	120	122	118	130
	3	C	120	116	116	134	130	124	120
	4	E	120	114	110	112	120	120	120
	5	D	116	120	130	118	132	120	130
14	1	A	140	132	126	136	128	124	138
	2	D	138	128	132	124	130	130	134
	3	E	130	130	130	130	130	128	132
	4	C	132	132	132	132	130	126	130
	5	B	134	134	140	136	130	134	130
15	1	D	110	100	100	104	116	110	114
	2	E	98	104	100	104	110	106	108
	3	A	100	102	98	100	100	98	102
	4	B	98	94	98	98	100	100	110
	5	C	104	108	108	104	100	102	110
16	1	A	150	130	140	140	140	140	140
	2	E	130	126	130	134	130	140	130
	3	D	146	138	136	136	140	140	140
	4	C	130	130	130	138	136	136	144
	5	B	150	150	140	138	136	138	136

Table of Systolic Blood Pressure Readings (mm.Hg) (cont'd.)

Subject	Round	Medication Code	Pre medication 40 min	Pre medication 20 min	Pre medication 0 min	Post medication 15 min	Post medication 20 min	Post medication 60 min	Post medication 120 min
17	1	D	100	90	104	88	94	98	98
	2	A	98	100	90	94	88	92	98
	3	B	98	92	92	90	88	88	88
	4	E	98	92	90	98	94	90	94
	5	C	100	92	92	96	92	100	90
18	1	C	120	118	122	118	122	116	120
	2	D	118	118	118	114	110	112	116
	3	E	122	110	112	116	116	130	122
	4	B	120	120	120	118	120	112	126
	5	A	116	110	116	118	114	110	126
19	1	B	98	98	100	104	98	100	98
	2	C	90	90	90	98	104	98	90
	3	A	100	92	96	98	100	98	100
	4	D	94	110	96	110	94	108	110
	5	E	114	110	104	108	116	120	114
20	1	E	120	114	112	114	116	112	120
	2	B	108	108	108	100	100	102	100
	3	C	110	110	106	110	106	106	112
	4	A	108	108	110	104	100	108	112
	5	D	110	110	110	110	106	106	112

Medication Code

A = Placebo
B = 10 mg. Neo-Synephrine
C = 25 mg. Neo-Synephrine
D = 50 mg. Neo-Synephrine
E = 100 mg. Neo-Synephrine

Table of Diastolic Blood Pressure Readings (mm.Hg)

Subject	Round	Medication Code	Pre medication 40 min	Pre medication 20 min	Pre medication 0 min	Post medication 15 min	Post medication 20 min	Post medication 60 min	Post medication 120 min
01	1	D	80	70	70	70	64	72	72
	2	B	70	68	60	60	64	70	64
	3	C	68	70	60	66	60	72	70
	4	E	68	70	62	66	64	64	60
	5	A	68	66	66	70	70	68	68
02	1	E	80	70	80	80	76	78	80
	2	D	80	80	72	70	70	70	80
	3	A	70	64	68	70	70	78	80
	4	C	78	72	76	80	70	76	70
	5	B	84	80	80	70	74	76	70
03	1	A	86	74	74	74	74	80	70
	2	C	74	78	80	70	70	70	80
	3	E	80	80	80	80	80	80	80
	4	B	82	80	82	80	74	78	72
	5	D	90	80	80	72	72	74	86
04	1	B	64	64	70	68	64	60	62
	2	E	70	70	80	70	60	64	70
	3	D	70	60	60	62	68	60	64
	4	A	60	60	50	60	66	60	64
	5	C	70	60	60	60	62	60	68
05	1	C	74	70	74	80	80	80	78
	2	A	70	74	76	76	80	80	80
	3	B	78	80	78	78	80	80	80
	4	D	80	70	70	70	70	80	80
	5	E	72	72	72	70	62	72	80
06	1	B	90	90	90	94	92	90	90
	2	E	80	80	80	80	90	90	90
	3	C	80	78	78	88	90	90	90
	4	D	90	90	100	100	90	90	90
	5	A	96	96	90	96	96	92	98
07	1	A	64	70	60	62	64	70	78
	2	C	64	60	68	64	64	62	70
	3	B	70	70	70	68	66	72	70
	4	E	60	60	70	80	78	80	70
	5	D	66	60	68	76	68	80	80
08	1	E	64	70	64	70	70	80	70
	2	D	74	70	70	70	70	70	70
	3	A	80	70	70	72	80	78	80
	4	C	70	70	70	70	66	80	74
	5	B	62	68	68	68	70	70	80

Table of Diastolic Blood Pressure Readings (mm.Hg) (cont'd.)

Subject	Round	Medication Code	Pre medication -5 min	Pre medication 20 min	Pre medication 0 min	Post medication 15 min	Post medication 20 min	Post medication 60 min	Post medication 120 min
09	1	C	70	70	64	76	70	80	88
	2	B	80	70	80	80	70	82	78
	3	D	74	70	70	70	70	84	90
	4	A	78	70	70	70	80	76	70
	5	E	80	80	76	78	68	70	70
10	1	D	70	70	70	62	70	64	86
	2	A	80	70	70	80	72	70	80
	3	E	78	64	70	64	80	74	80
	4	B	68	60	60	68	60	60	70
	5	C	70	70	70	66	66	68	70
11	1	E	60	60	60	74	70	68	80
	2	C	58	60	60	60	64	68	62
	3	B	56	56	56	56	60	72	60
	4	D	60	60	56	56	68	64	64
	5	A	52	60	58	60	64	60	60
12	1	C	70	70	74	70	70	80	70
	2	B	70	64	70	70	76	68	62
	3	D	62	62	70	68	70	70	70
	4	A	76	64	60	60	68	68	70
	5	E	62	60	60	60	70	84	76
13	1	B	84	84	80	80	90	88	90
	2	A	84	76	80	80	76	80	90
	3	C	90	80	80	100	98	88	90
	4	E	80	70	80	80	88	90	90
	5	D	76	80	84	78	80	84	84
14	1	A	80	76	62	76	72	74	76
	2	D	74	68	70	76	80	88	88
	3	E	82	80	80	90	90	90	90
	4	C	80	78	80	76	80	80	90
	5	B	90	84	90	84	82	84	90
15	1	D	64	64	70	70	80	74	70
	2	E	60	70	60	70	74	64	72
	3	A	62	62	68	68	68	66	70
	4	B	60	64	60	68	64	70	72
	5	C	70	70	70	60	60	62	80
16	1	A	100	100	100	108	100	98	100
	2	E	90	90	90	100	90	100	90
	3	D	98	100	96	100	90	92	100
	4	C	90	90	90	90	100	100	100
	5	B	90	100	100	100	96	100	100

Table of Diastolic Blood Pressure Readings (mm.Hg) (cont'd.)

Subject	Round	Medication Code	Pre medication 40 min	20 min	0 min	Post medication 15 min	20 min	60 min	120 min
17	1	D	70	70	70	60	70	72	70
	2	A	60	60	60	70	60	64	70
	3	B	56	60	60	56	60	60	64
	4	E	60	68	60	60	60	60	60
	5	C	62	58	60	60	60	60	68
18	1	C	72	70	70	70	76	76	80
	2	D	74	70	70	68	74	74	70
	3	E	72	70	70	80	80	88	84
	4	B	70	70	70	70	70	70	80
	5	A	70	78	70	76	74	70	70
19	1	B	50	60	60	60	64	66	60
	2	C	58	60	60	68	64	70	60
	3	A	56	60	70	60	60	60	60
	4	D	50	70	56	64	60	68	70
	5	E	56	64	60	62	62	64	66
20	1	E	70	70	64	76	80	80	80
	2	B	70	68	74	68	68	70	70
	3	C	70	64	70	66	70	74	80
	4	A	70	68	68	80	70	78	70
	5	D	70	70	70	68	76	80	80

Medication Code

A = Placebo
B = 10 mg. Neo-Synephrine®
C = 25 mg. Neo-Synephrine®
D = 50 mg. Neo-Synephrine®
E = 100 mg. Neo-Synephrine®

REFERENCE 24

Bickerman, H. A., “Physiologic and Pharmacologic Studies on Nasal Airway Resistance (R_N),” The Proprietary Association. Current Research Methodology in the Evaluation of Proprietary Medicines: *Proceedings of a conference sponsored by the Scientific Development Committee of the Proprietary Association*, 1971

REFERENCE 25

Thomas, S.H.L., K. L. Clark, R. Allen, and S.E. Smith, “A Comparison of the Cardiovascular Effects of Phenylpropanolamine and Phenylephrine Containing Proprietary Cold Remedies,” *British Journal of Clinical Pharmacology* 32:705-711, 1991.

REFERENCE 26

[redacted] Dr. Surrey Dr. Berberian Dr. Poley
[redacted] -Dr. Wess[redacted]er Dr. Dennis
Mr. St[redacted]er Dr. Gerding Mr. Auerbach-Mr. Pratt June 26, 1968
Dr. Lands Dr. Cox (3) Mrs. Graham-Mrs. Arnsdorff-Mrs. Jordan

Memo to: Dr. Hulme
J.G.Bird

Subject: Neo-Synephrine Oral - In-House Pulse and Blood Pressure Study
(Ref.: Hulme to Berberian, Apr. 1 and to Bird, Apr. 3,'68)

Your protocol and arrangements for the above study were followed by Dr. Berberian, Mrs. Graham, R.N., Mrs. Arnsdorff, R.N., and Mrs. Jordan. Mr. Stander has written his analysis of the results in his memo to me of June 19, attached.

On my request, Mrs. Graham supplied the names, age, body weight and sex of the 20 volunteers (see Table 1). All were males as you arranged in concert with a previous, analogous study, described by Dr. Luduena to Dr. Suter, Oct. 18, 1966, and by Mr. Stander to Dr. Luduena, Jan. 5, 1967. Mr. E.L.Pratt (see attached memo to M. E. Auerbach, June 17, 1968) has supplied for the present study the weights of the drug in each of four randomly selected individual capsules at each dose level employed. Variations in body weight and among capsules should be born in mind in interpreting the results. A description of the protocol and an analysis of the results are presented in Mr. Stander's analysis, attached. His memo, dated June 19, 1968, should be read prior to the comments which follow.

Comments

Preliminary Remarks

The variation in body weight are widely and rather smoothly distributed between 140 and 225 pounds (see Table 1). Each subject received each medication at the doses described regardless of weight. Larger standard errors may be expected than if the dose per pound were in a narrow range. A statistically significant difference is only occasionally found in the responses.

The assays of Neo-Synephrine HCl (see Table 2) in 2 of 4 capsules for which the labels claimed 25 mg overlapped one of 4 from the 20 mg stock. For the former 4, the range was 101 to 111 per cent of claim (20 mg) and for the latter, 84.3 to 103 per cent of claim (25 mg).

It is conceivable that more pairs of values would have been significantly different, and the means further apart, if dosage per unit of body weight had a narrow range, and if label claims for the 25 mg capsules had been more accurately met or proven. The ages of the subjects varied between 24 and 49 years. This variability may have little or no effect upon the analysis of the responses. This and the wide range of body weights are at least in keeping with the actual OTC "practice".

Interpretations

There were only four post-medication values for Neo-Synephrine showing statistical significance, out of a total of 36 values. Since two of these show an inverse* relationship (see pulse rates at 30 minutes after the 15 and "25" mg doses) and since the other two reach statistical significance only at the 120 minute period, there seems to be little or no "clinical importance"**in

* dose-response
** see footnote-page 3

such values. It would therefore appear that in this experiment there are no changes in any pre-medication parameter which are sufficiently consistent with other appropriate data in the results to justify the conclusion that any of the three doses of Neo-Synephrine produced statistically significant responses which should be dependably reproduced if the experiment were repeated. Caprice may have "located" the four significant differences from placebo values. Caprice could show such significant changes in other places in the results in a repeated experiment of the same demographic data, etc.

The highly significant changes in the 20 and 0 (zero) minute values for systolic and diastolic blood pressure as compared with the 40 minute values prior to medication (all data being pooled from all 5 test periods), although the means themselves are only slightly different, may be interpreted as demonstrating careful and accurate measurement of blood pressure throughout the experiment. Such accuracy in pulse rate recording is not suspect despite the absence of statistically significant changes in this parameter, for it is considered more accurately measurable than blood pressure, especially the diastolic levels. The subjects were kept very quiet, inactive and undisturbed throughout all observation periods, this precaution thus contributing, along with careful measurements by the nurses, to the significant, expected, although slight downward trend in pre-Rx B.P. values and the proper recording of all post-medication values, whether statistically significant or not.

If one views the data without regard for presence or absence of significant differences as analyzed, one may see the following: pulse rates after placebo continue to fall for 60 minutes (continued rest may explain). The same is true following all medications, including phenylpropanolamine.* These changes must be considered "trends" except where statistical significance is shown. These "trends" are sufficiently consistent and of such time-related rate to justify their mention but only with reservation unless examined for true significance. This does not appear to be applicable to the data for systolic blood pressure. Phenylpropanolamine significantly increases systolic pressure at the 60 and 120 minute periods by approximately 4 and 7 per cent respectively. On the other hand all medications including the placebo are consistently followed by a moderate "trend" in increase in diastolic pressure for 120 minutes. Statistical significance in this increase only appeared once, at 120 minutes following 15 mg of Neo-Synephrine.

In the previous study arranged by Dr. Luduena, the 25 mg dose produced a significant decrease in pulse rate 60 minutes after medication and, in the present study, at 30 minutes. This dose produced no significant changes in systolic or diastolic B. P. in either study. Thus the two experiments are rather compatible as far as they can be compared, including pre-medication data for pulse rates and B.P. and also for post-placebo responses. Only the 25 mg dose of Neo-Synephrine was common to the two trials.

Conclusions

Within the limits of the present experiment which was carefully conducted at the clinical level there are but few, isolated points at which statistically significant effects on pulse rates and blood pressure were produced by 15, 20 or 25 mg label-claim, oral doses of Neo-Synephrine HCl. Viewed for consistency and compatibility with all other appropriate data in this experiment, these points (6 of 32 possible points) do not justify conclusions that "clinically important"

* HCl

effects have been produced by these doses of the drug. Wide variations in body weight and some reported modestly high (mean and range) values for actual drug content in the 20 mg capsules and moderately low values for the 25 mg capsules (4 at all dose-levels were individually analyzed) may have precluded the demonstration of more significance among the data. However, the weights of prospective customer-patients should vary even more than those of the volunteers in this study, hence the study bears an approximate relationship to market-place conditions.

Phenylpropanolamine at the only dose employed, 50 mg, produced a statistically significant increase in systolic blood pressure only at the 60 and 120 minute periods following its ingestion whereas no dose of Neo-Synephrine did so at any time period studied. Phenylpropanolamine produced no statistically significant changes in pulse rates or diastolic pressure. It was not used in the previous study. The same condition of body weight variation applies to its use in the present trial. The two higher doses of Neo-Synephrine used in the previous study (also all males) produced a few statistically significant decreases in pulse rates (at 60 minutes following 50 mg and at 30 and 60 following 100 mg). The 100 mg dose significantly elevated systolic blood pressure 30 and 60 minutes following its ingestion. These results appear plausible and dose- and time-related. These doses did not significantly alter diastolic pressure, and not even a trend was seen which was different from that following the placebo.

Summary

In 20 males with ages ranging between 24 and 49 years and weights between 140 and 225, a well-executed cross-over trial employing a placebo, 15, 20 and 25 mg single oral capsuled doses of Neo-Synephrine® Hydrochloride and 50 mg single oral doses of phenylpropanolamine*was conducted. Pulse rates and systolic and diastolic blood pressure at -40, -20, 0, and+15 +30, +60 and +120 minutes were recorded for all medications and placebo. Although a few scattered changes among the post-medication values for Neo-Synephrine were found to be statistically significant, certain of these were either reverse-dose-related, or were seen only at the 120 minute period and not matched by a similar change at one or both higher doses. Thus it is suggested that these changes (none exceeding 5.7 per cent from placebo values) are of little or no clinical importance. Phenylpropanolamine hydrochloride in single oral, capsuled doses of 50 mg. likewise produced few (2) statistically significant changes. These were only in systolic blood pressure (nearly 4 and 7 per cent increases at 60 and 120 minutes, respectively) but appear plausible.

The overall impression of the undersigned is that no effects have,within the limits of this experiment, been reliably demonstrated following single oral doses of 15, 20 or 25 mg of Neo-Synephrine® Hydrochloride, as regards pulse rates and blood pressure. There were no remarkable changes in these parameters in any individual subject.

J. G. Bird

* HCl

The use of the term "no clinical importance" in this memo does not preclude possib significant effects of any of the medications upon nasal air resistance, studied elsewhere but not in these trials.

Table 1

Subject No. [a]	Age [b]	Weight, pounds [c]
1	38	140
2	48	161 1/2
3	46	143 1/2
4	35	179
5	26	173
6	44	181
7	24	186 1/2
8	28	164 1/2
9	39	212 3/4
10	49	204
11	45	173 1/2
12	40	199
13	29	161
14	27	154
15	25	225
16	36	150
17	44	155
18	35	155 1/2
19	31	145 3/4
20	26	151 3/4

a) All males
b) Range 24-48 years
c) Range 140-225 lbs.

REFERENCE 27

Elis, J., D. R. Laurence, H. Mattie, and B. N. C. Pritchard, “Modification by Monoamine Oxidase Inhibitors of the Effect of Some Sympathomimetics on Blood Pressure,” *British Medical Journal* 2:75-78, 1967.

REFERENCE 28

Rodgers, J. M., E. B. Reilly, and H. A. Bickerman, “Physiologic and Pharmacologic Studies on Nasal Airway Resistance,” *Clinical Pharmacology and Therapeutics* 14:146, 1973.

REFERENCE 29

Kanfer, I., R. Dowse, and V. Vuma, “Pharmacokinetics of Oral Decongestants,” *Pharmacotherapy* 13::116S – 128S, 1993.

REFERENCE 30

Martinsson, A., S. Bevegard, and P. Hjemdahl, “Analysis of Phenylephrine in Plasma: Initial Data about the Concentration-Effect Relationship,” *European Journal of Clinical Pharmacology* 30:427-431, 1986.

REFERENCE 31

Cavallito, C. J., L. Chafetz, and L. D. Miller, “Some Studies of a Sustained Release Principle,” *Journal of Pharmaceutical Sciences* 52:259-263, 1963.

REFERENCE 32

pared with Ephedrine in a Double-Blind Study," (English translation), ("Neseril, ett nytt nasdroppspreparat, och efederin, jamforda med dubbel-blindteknik"), *Svenska Laekartidningen*, 61:3204–3212, 1964.

(6) Harris, H. H., "Comparative Study of Decongestive Effectiveness of Oxymetazoline Hydrochloride in Rhinitis," *The Eye, Ear, Nose and Throat Digest*, 46:41–43, 1967.

(7) Green, M., "Double-Blind Study of Nasal Decongestion with Oxymetazoline and Phenylephrine in Asthmatic Children with Rhinitis," *Review of Allergy*, 20:863–868, 1966.

(8) Cohen, B. M. and E. P. Duffy, "Physiologic and Clinical Estimates of the Relief of Nasal Flow Obstruction in Allergic Rhinitis: Effects of a Topical Decongestant (Oxymetazoline)," *The Journal of Asthma Research*, 7:65–73, 1969.

(9) Summary of Animal Safety Data is included in OTC Volume 040298.

(10) Summary of Human Safety Data is included in OTC Volume 040298.

(11) Neidorff, A. H., "Clinical Note: Double-Blind Comparison of the Duration of Effect of Oxymetazoline and Phenylephrine in Children," *Annals of Allergy*, 24:250–251, 1966.

d. *Phenylephrine hydrochloride (oral/topical)*. The Panel concludes that phenylephrine hydrochloride is safe and effective as an oral and as a topical nasal decongestant for OTC use as specified in the dosage section discussed below.

(1) *Safety.* (i) *As an oral nasal decongestant:* Clinical experience has confirmed that phenylephrine hydrochoride is safe in the dosage ranges used as an oral nasal decongestant.

Key and Violante reported that oral doses of 40 to 60 mg phenylephrine are necessary for consistent clinically meaningful cardiovascular effects such as increased diastolic pressure and reflex cardiac slowing (Ref. 1). Various reports reinforce the impression that in normal volunteers, blood pressure and pulse rate responses to 10 to 15 mg oral doses are equal to or only minimally greater than placebo. The maximum blood pressure increase does not exceed 2 to 7 mm Hg and the pulse rate changes do not exceed ±6 beats/minute. At doses of 25 mg, blood pressure increases up to 7 mm Hg and pulse changes of ±4–13 beats per minute were occasionally noted at some time intervals (Refs. 1 through 11). If patients were also receiving MAO inhibitors, however, even 10 mg doses of phenylephrine can induce clinically significant cardiovascular responses (Ref. 12).

Overtly perceived side effects at 10-mg doses approximate the incidence and pattern of a placebo response, whereas 15 to 25-mg doses are associated with an increasing incidence of symptoms related to mild central nervous system stimulation (Ref. 1).

(ii) *As a topical nasal decongestant:* Clinical experience has confirmed that phenylephrine hydrochloride is safe in the dosage ranges used as a topical nasal decongestant. Gundrum, Stambuck and Gaines reported a study in which supratherapeutic doses of 0.25 percent phenylephrine drops were chronically administered to rabbits (Ref. 13). The animals were given drops in each nostril either 3 times daily for 10 days or 10 times daily for 3 days. Examination of nasal tissue sections removed from these treated animals revealed no gross or microscopic changes from normal nasal mucosa.

Objective measurement studies showed transient rebound congestion in 3 of 12 adult rhinitis patients during 3 days of treatment with 0.5 percent phenylephrine spray (Ref. 14). Two thirds of 92 chronic rhinitis patients using 0.25 percent phenylephrine spray for 2 weeks noted rebound congestion (Ref. 15). Rhinoscopic observation revealed rebound congestion in 4 of 33 children following single doses of 0.25 percent phenylephrine drops, 5 drops in each nostril (Ref. 16).

Groups of patients with either cardiac, hypertensive and hyperthyroid disorders or diabetes mellitus were administered 5 drops of 0.25 percent or 1 percent phenylephrine solution into each nostril remaining in a head-low position for several minutes to maximize contact time (Refs. 17 and 18). No marked changes in blood pressure control readings were noted over a 45-minute observation period.

(2) *Effectiveness.* (i) *As an oral nasal decongestant:* Clinical studies have documented the effectiveness of phenylephrine as an oral nasal decongestant.

A series of five double-blind crossover placebo-controlled studies over a 3-year period in one laboratory revealed oral doses of phenylephrine from 5 to 25 mg to induce objectively measurable nasal decongestion when compared to placebo in patients with head cold as determined by an anterior rhinometry procedure (Refs. 5 through 9, and 19). Onset time was in 15 to 20 minutes with a duration of 2 to 4 hours. Maximum nasal decongestant effect was associated with the 25 mg dose. Two other laboratories conducted five similarly designed experiments, but because of greater apparent placebo response and variability in inpatient response the studies could not demonstrate a statistically significant difference of 10 to 25 mg from placebo (Refs. 20 through 24).

Subsequent studies measuring nasal airway resistance in head cold patients demonstrated significant nasal decongestant responses to 10 to 25 mg phenylephrine (Ref. 10). In these studies, 25 mg induced a maximal reduction of nasal resistance approaching that reported for noncongested normals, and 10 to 15 mg doses were clinically equivalent in inducing a decrease of nasal resistance about ⅔ maximal. Onset of these effects occurred within 15 minutes. The maximum effect occurred within 30 to 90 minutes with a gradual decline thereafter. A double-blind crossover study in 20 chronic rhinitis patients, however, could demonstrate no significant decrease in nasal airway resistance as compared to placebo with 10, 20, or 40 mg of phenylephrine, orally, over a 4-hour observation period (Ref. 25). In this study, phenylpropanolamine 40 mg and pseudoephedrine 60 mg each produced a significant decrease in nasal airway resistance persisting for at least 3 hours.

A recent double-blind controlled study involving 50 adult patients with nasal congestion associated with the "common cold" (25 patients in each group) demonstrated that a single oral 10 mg dose of phenylephrine led to a reduction in nasal airway resistance averaging 11 percent at 15 minutes, 21 percent at 30 minutes, 28 percent at 60 minutes and 26 percent at 120 minutes (Ref. 26). These reductions were all significantly different from placebo at the corresponding measurement times. These 50 patients were part of a 200-patient subjective evaluation study group with nasal congestion associated with the "common cold", 100 of each who received either 10 mg phenylephrine or placebo at 4-hour intervals over a 12-hour period. Patient subjective evaluation revealed that the phenylephrine treatment group experienced relief of nasal congestion, runny nose and sneezing throughout the 12-hour observation period. Symptom relief in each case was significantly different from that reported by the placebo group (Ref. 26).

(ii) *As a topical nasal decongestant:* In a double-blind crossover placebo-controlled study, phenylephrine was given as a 0.5 percent spray, 1 spray in each nostril repeated in 3 minutes, to one group of 16 patients with head cold and one group of 9 patients with allergic rhinitis. Objective measurements using both posterior electronic rhinometry and body plethysmography revealed significant nasal decongestion at the 30- and 60-minute recording times (Ref. 27).

In another study using 0.5 percent phenylephrine spray in 12 adult rhinitis patients, objectively measured nasal decongestant effects persisted from 1 to 3 hours following administration (Ref. 14). In a 2-week subjective evaluation study of phenylephrine 0.25 percent spray in 92 chronic rhinitis patients, the duration of effect following each dose was generally reported to be 4 hours or less (Ref. 15).

(3) *Dosage.* (i) *As an oral nasal decongestant:* Adult oral dosage is 10 mg every 4 hours not to exceed 60 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 mg every 4 hours not to exceed 30 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 mg every 4 hours not to exceed 15 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(ii) *As a topical nasal decongestant:* Adult topical dosage is 2 to 3 drops or sprays in each nostril of a 0.25 to 0.5 percent aqueous solution not more frequently than every 4 hours. Children 6 to under 12 years topical dosage is 2 to 3 drops or sprays in each nostril of a 0.25 percent aqueous solution not more frequently than every 4 hours. Children 2 to under 6 years topical dosage is 2 to 3 drops in each nostril of a 0.125 percent aqueous solution not more frequently than every 4 hours. Only drops should be used in children 2 to under 6 years since the spray is difficult to use in the small nostril. For children under 2 years, there

REFERENCE 33

Hengstmann J. H. and Gorozny, J., “Pharmacokinetics of ^{3}H-Phenylephrine in Man,” *European Journal of Clinical Pharmacology* 21:335-341, 1982.

ATTACHMENT 1

Joint Meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee
October 18-19, 2007

This is the final report of the joint meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee held on October 18-19, 2007. A verbatim transcript will be available in about 2 weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac/cder07.htm

All external requests for the meeting transcripts should be submitted to the CDER Freedom of Information office.

The Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee of the Food and Drug Administration met on October 18-19, 2007 at the National Labor College, 10000 New Hampshire Ave., Silver Spring Maryland. Mary Tinetti M.D. and Marsha D. Rappley, M.D. chaired the meeting. There were approximately 400 in attendance.

Attendance:

Nonprescription Drugs Advisory Committee Members present (voting):
Mary E. Tinetti, M.D., Ernest B. Clyburn, M.D., Ruth M. Parker, M.D., Robert E. Taylor, M.D., Ph.D., F.A.C.P; Ralph B. D'Agostino, Ph.D., Marie R. Griffin, M.D., Jan L. Hewett, J.D., B.S.N., William H. Shrank, M.D., M.S.H.S.

Nonprescription Drugs Advisory Committee Member absent :
Garret A. FitzGerald, M.D.

Pediatric Advisory Committee Members present (voting):
Marsha D. Rappley, M.D., Dennis Bier, M.D., Avital Cnaan, Ph.D., M.S., Robert S. Daum, M.D., Leon Dure, M.D., Thomas Newman, M.D., M.P.H., Geoffrey L Rosenthal, M.D., Ph.D.,

Pediatric Advisory Committee Members absent:
Michael E. Fant, M.D., Ph.D., Melissa Maria Hudson, M.D., Keith Kocis, M.D., M.S., Robert Ward, M.D.

Temporary Voting Members:
Thomas P. Atkinson, M.D., Ph.D., William J. Calhoun, M.D., F.A.C.P., Amy J. Celento-Stamateris *(Patient/ Family Representative),* Michael R. Cohen, R.Ph., M.S., D.Sc., Sean P. Hennessy, Pharm.D., Ph.D., Jesse Joad, M.D., Richard A. Neill, M.D.

Temporary Member (non-voting)
Richard L. Gorman, M.D. *(Pediatric Health Organization Rep.)*

Industry Representatives: (non-voting):
George S. Goldstein, M.D. (NDAC), Elizabeth A. Garofalo, M.D (PAC).

FDA Participants:
John Jenkins, M.D., Charles Ganley, M.D., Joel Schiffenbauer, M.D., Robert Nelson, M.D., Ph.D., Ann W. McMahon, M.D., M.S.

Open Public Hearing Speakers:
Anthony R. Temple, M.D., F.A.A.P., David I. Bromberg, M.D., F.A.A.P., Winnie Landis, R.Ph., Patricia Jackson Allen, R.N., M.S., P.N.P., F.A.A.N., Peter Lurie, M.D., M.P.H., Daniel A. Mannello.

On October 18-19, 2007, the committees met in joint session to discuss the safety and efficacy of over-the-counter (OTC) cough and cold products marketed for pediatric use.

On October 18th, Mary Tinetti, M.D., (NDAC Chair) and Marsha D. Rappley, M.D., (PAC Chair), called the meeting to order at 8:00 a.m. The Committee members and the FDA participants introduced themselves. The conflict of interest statement was read into the record by Darrell Lyons, BSN, Designated Federal Officer (DFO). The Agenda for the meeting was as follows:

8:00	Call to Order Introduction of Committee	**Mary Tinetti, M.D.** Chair, Nonprescription Drugs Advisory Committee
		Marsha D. Rappley, M.D. Chair, Pediatric Advisory Committee
	Conflict of Interest Statement	**Darrell Lyons, BSN, RN** Designated Federal Official
8:30	OTC Cough and Cold Products: Use in Children	**Joel Schiffenbauer, M.D., Deputy Director** Office of Nonprescription Products CDER, FDA
8:40	Regulatory History of Pediatric Cough/Cold Products	**Marina Y. Chang, R.Ph., Team Leader** Office of Nonprescription Products CDER, FDA
	PETITIONER PRESENTATIONS	
8:55	Cough and Cold Preparations for Young Children: Overview and Petition	**Joshua M. Sharfstein, M.D.** Commissioner of Health, Baltimore City
	Efficacy of Cough and Cold Preparations for Young Children	**Wayne R. Snodgrass, M.D., Ph.D.** Professor, University of Texas Medical Branch
	Safety of Cough and Cold Preparations in Young Children	**Michael Shannon, M.D., M.P.H.** Professor of Pediatrics, Harvard Medical School
	Cough and Cold Preparations in Young Children: Practical Considerations	**Daniel J. Levy, M.D.** President, MD Chapter, American Academy of Pediatrics
10:00	***Break***	
10:15	**INDUSTRY PRESENTATIONS**	
	Introduction	**Linda Suydam, D.P.A.** President Consumer Healthcare Products Association

	Efficacy Research	**Phil Walson, M.D.** University of Cincinnati Pediatrician
	Pharmacokinetics	**Cathy Gelotte, Ph.D.** McNeil Consumer Healthcare
	Safety	**Richard Dart, M.D.,** Rocky Mountain Poison and Drug Center & **Ed Kuffner, M.D.** McNeil Consumer Healthcare
	Industry Commitments & Recommendations	**Linda Suydam, D.P.A.** President, Consumer Healthcare Products Association
12:00	***Lunch***	
	FDA PRESENTATIONS	
1:15	Clinical Pharmacology Perspectives of Pediatric Dosing of OTC Cough & Cold Medicines	**Partha Roy, Ph.D., Senior Clinical Pharmacologist** Office of Clinical Pharmacology CDER, FDA
1:35	Considerations for Extrapolation of Efficacy from Adults to Children; Examples and Experience from the Division of Pulmonary & Allergy Products	**Peter Starke, M.D., Associate Director for Safety &** **Charles E. Lee, M.D., Medical Team Leader** Division of Pulmonary & Allergy Products CDER, FDA
1:50	Literature Review: Safety and Efficacy of OTC Cough/Cold Drug Products in Pediatric Patients	**Lolita A. Lopez, M.D., Medical Officer** Office of Nonprescription Products CDER, FDA
2:05	Adverse Events and Poisonings Associated with Cough and Cold Products in Children Less Than 6 Years of Age	**Gita Akhavan-Toyserkani, Pharm.D., MBA, Safety Evaluator** Office of Surveillance and Epidemiology, CDER, FDA
2:30	Over-the-Counter Cough/Cold Products Medication Errors	**Richard Abate, R.Ph., M.S., Safety Evaluator** Office of Surveillance and Epidemiology, CDER, FDA
2:45	*Questions for Speakers*	
3:15	***Break***	
3:45	*Questions for Speakers/Committee Discussion*	
5:00	***Adjourn***	

October 19, 2007

8:00	Call to Order Introduction of Committee	**Mary Tinetti, M.D.** Chair, Nonprescription Drugs Advisory Committee
		Marsha D. Rappley, M.D. Chair, Pediatric Advisory Committee *(via telephone)*
	Conflict of Interest Statement	**Darrell Lyons, BSN, RN** Designated Federal Official
8:30	*Open Public Hearing*	
10:30	***Break***	
10:45	*Questions and Panel Discussion*	
12:00	***Lunch***	
1:15	*Questions and Panel Discussion*	
4:00	***Adjourn***	

Questions to the Committee:

The Agency has received a Citizen Petition requesting that FDA take action to re-label the OTC cough and cold products. The Petition states that these products are not safe or effective in children under the age of 6 years for treatment of cough and colds. The efficacy of the cough and cold ingredients was based on the extrapolation of efficacy from adults using a fraction of the adult dose. It should be noted that although the petitioners are requesting that the Agency take action on products for children less than 6 years of age, efficacy has also been extrapolated for children less than 12 years of age. Therefore, any actions recommended for children less than 6 may also apply to children less than 12 years of age.

The products regulated under the Final Monograph are considered to be Category I products, GRASE (generally recognized as safe and effective). If a decision is reached to require new studies for these products, rule making would be needed to re-categorize these ingredients to Category II (Not generally recognized as safe and effective) and sponsors would have the opportunity to perform these studies. If new studies are requested and do not establish efficacy or safety then products would be required to discontinue marketing.

1. Efficacy

a. Discuss the available published studies and how they inform our knowledge regarding the efficacy of the monograph cough/cold products for the common cold in children.

Committee Discussion:

The committee felt that the published studies that were available did not demonstrate efficacy due to a number of reasons. The studies had limitations, they were few in number, the sample sizes were too small, and the studies were underpowered with inappropriate outcomes. The committee recommended more studies and data. (See Transcript for Complete Discussion)

b. Is it appropriate to extrapolate data from adults to children or from older children to younger children for the cough and cold indications (yes/ no)? In answering, please consider whether the pathophysiology of the disease is similar in adults and children. If extrapolation is acceptable;

-please comment on when extrapolation would be appropriate.

-please comment on what additional PK studies should be conducted in order to better inform extrapolation for individual ingredients.

Committee Discussion:
For a point of clarification the committee defined and categorized children into two groups: (1) less than 2 years of age and (2) 2 years to less than 12 years of age; the committee further proposed changes in the wording of the question to:

1. Is it appropriate to extrapolate data from adults to children, less than 2 years old, for the cough and cold indications in the common cold?
Yes: 0 **No: 22** **Abstain: 0**

2. Is it appropriate to extrapolate data from adults to children, 2 years to less than 12 years old, for the cough and cold indications in the common cold?
Yes: 1 **No: 21** **Abstain: 0**

3. Is it ever appropriate to extrapolate efficacy data within the childhood population, i.e., age 2 to less than 12 years of age, for the cough and cold indications in the common cold?
Yes: 4 **No: 18** **Abstain: 0**

c. If extrapolation is not considered appropriate for cough/cold ingredients for common cold indications, please describe the data needed to demonstrate efficacy in children. For example, would clinical studies in children with clinical endpoints be necessary to support efficacy in children (yes/no)? If clinical trials are determined to be necessary, please comment on which ingredients and for which age groups.

The committee proposed to change the wording of the question to:
Would clinical studies, in children less than 12 years old, with clinical endpoints be necessary to support efficacy in children less than 12 years old?
Yes: 22 **No: 0** **Abstain: 0**

Committee Discussion:
The Committee agreed that clinical trials should focus on single ingredient studies with clear clinical endpoints that are pathophysiologically related to what the drug is expected to do, and that each ingredient should be studied one-by-one in children. The clinical endpoints used should include cough/cold symptoms, specifically, those for which the products are marketed for children. Sleep/sedation should not be an endpoint. Pharmacokinetic studies of single ingredients are also needed. (See Transcript for Complete Discussion).

2. Safety
The safety discussion in the petition focuses on cases of misuse, unintentional overdose, and excessive dosing of OTC cough and cold drug products. The petition does not specifically address the safety of OTC cough and cold drug products for children under the age of 6 years when used in accordance with the labeled instructions and under a physicians care. Considering the widespread use of OTC cough and cold products over decades, there are reported cases of serious adverse events. We are interested in understanding why these events happen and would like to be able to reduce the occurrence of preventable events.

a. Aside from the issue regarding excessive dosing, please comment on any significant safety issues that can be identified when these drugs are used at the currently recommended doses.

Committee Discussion:
The committee noted that the marketing of products with multiple ingredients and current product labeling is confusing; both lead to issues with the safe use of the products by the consumer. Also, the lack of standardization in dosing and, dosing devices, and dosing by age rather than by weight are significant safety concerns.
(See Transcript for Complete Discussion)

What additional safety data, if any, are needed to better understand the safety of these ingredients in children?

Committee Discussion:
The data suggest an increase in seizures, particularly in the 6-12 year old age group. The committee discussed the importance of determining whether these noted seizures represent adverse effects of the cold/cough medications or febrile seizures or other. Better estimates of the rates of adverse events of cough/cough medications are needed, although the committee recognized the difficulty in ascertaining these estimates. The committee recommended the following actions be taken: a further review of the existing safety data; the conduct of large, simple safety trials; the conduct of rigorous case control design and large post-market trials; and, surveillance that is more systematic than the current FDA postmarketing surveillance. The committee also

recommended standardization of dosing regimens, standardization of dosing devices, standardization of label wording, and standardized product units of measures. (See Transcript for Complete Discussion)

What actions do you recommend the agency consider in order to reduce the occurrence of adverse events related to factors associated with the drug (e.g., known toxicities) or the age group (e.g., variations in metabolism, variations in weight)? *(See Transcript for Complete Discussion)*

b. Please comment on the contribution of mis-dosing to the overall safety profile of these products for each age group, and how this should affect their availability as OTC drug products.

Committee Discussion:
The committee noted that according to the information in the FDA and Industry presentations, the highest chance for mis-dosing occurred when there was no dosing information available on the label. Therefore, the recommendation was for all products to list dosing instructions on the label for age groups for whom the medications are allowed. (See Transcript for Complete Discussion)

c. Should dosing devices be required with liquid formulations (yes/no)?

Committee Discussion:
The committee recommended standard wording for dosing, unit of measure, and concentration to reduce consumer errors and proposed changing the wording of the question to:

Should dosing devices that are standardized in wording and dosing be required with liquid formulations?
Yes: 22 No: 0 Abstain: 0
(See Transcript for Complete Discussion)

Should all dosing devices (cups, spoons, syringes, etc.) bear only calibrations corresponding to, and identified with the same unit of measure, for the specific dosages described on the package labeling (yes/no)?

Committee Discussion:
There was no vote for this question as the committee addresses this issue in question 2c. (See Transcript for Complete Discussion)

d. Please comment whether there are other formulations that will assist caregivers in providing the correct dose (for example, pre-measured drug). *(See Transcript for Complete Discussion)*

3. Based on the discussions regarding efficacy and safety, are there age groups for which these ingredients should not be used right now (yes/no)? If so, which age groups and ingredients?

Committee Discussion:
The committee proposed the following question:

a. Based on the discussions regarding efficacy and safety, should these ingredients (antihistamines, nasal decongestants, and antitussives) NOT be used now in children under the age of 2 for the common cold?
Yes: 21 No: 1 Abstain: 0

Committee members also expressed concerns that the safety data presented, suggested significant differences in the 2 to 6 year old child population. Therefore, the committee recommended voting on whether they should recommend children age 2 and less than 6 years old not use these products now prior to voting on the age 6 to less than 12 child population.
(See Transcript for Complete Discussion)

b. Should the committee recommend that these ingredients (antihistamines, nasal decongestants, and antitussives) NOT be used for the common cold right now for children between the ages of 2 and less than 6?
Yes: 13 No: 9 Abstain: 0

c. Should the committee recommend that these ingredients (antihistamines, nasal decongestants, and antitussives) NOT be used for the common cold right now for children between the ages of 6 and less than 12?
Yes: 7 No: 15 Abstain: 0

4. Labeling
Currently, the directions for some of the OTC cough and cold products such as the decongestants and antitussives, instruct a parent to "consult a doctor" for children under two years of age. The directions for OTC antihistamines instruct a parent to "consult a doctor" for children under 6 years of age. There is also professional labeling available for antihistamines for children between 2 and 6 years of age.

The "consult a doctor" or "ask a doctor" directions have permitted physicians to make clinical judgments about whether a specific OTC product was right for a child under their care. The labeling proposed in the petition would potentially limit the ability of physicians to prescribe OTC cough and cold products in children less than 6 years old and may also impact the labeling for children less than 12 years of age.

a. If there are age groups that should not use these products, discuss the language that should be used to convey this.

- The petitioner has recommended language: "These products have not been found to be safe and effective for children under 6 years of age for treatment of cough and cold. These products should not be used for treatment of cough and cold in children under 6 years of age". Do you agree with this wording (yes or no)?

- The Consumer Healthcare Products Association has recommended language for children less than 2 years of age: "Do not use". Do you agree with this wording (yes or no)? If these products are labeled with "Do not use" should this direction apply to consumers as well as to health care providers, such that no one will use these products?

- FDA regulations require the following labeling for antihistamines in children less than 6 years of age and all other ingredients in children less than 2 years of age: "Ask a doctor" or "Consult a doctor". Do you agree with this wording (yes or no)?

- Please discuss other labeling options we should consider.

Committee Discussion:
The committee determined that the Petitioner's recommended language was too complicated and that requires simplification in order to allow ease of reading and understanding by the consumer. The committee recommended that standardized language and warnings, and universal symbols be developed and implemented after testing with consumers and patients. Overall, the committee did not agree with the Petitioner's recommended labeling language and therefore, a vote on the first bulleted question above was not taken. (See Transcript for Complete Discussion)

b. We remind you that efficacy was also extrapolated for children less than 12 years of age. Should FDA consider similar labeling, as suggested by the petitioner for children less than 6 years of age, for children 6 - 11 years of age? Please respond yes or no. Discuss whether this would apply to all or only some ingredients. *(See Transcript for Complete Discussion)*

c. If you decide that the use of some products in children less than 2 years old is not prohibited, please discuss how these products for children less than 2 years of age should be labeled.

Committee discussion: *The committee voted unanimously that these products should be prohibited in children less than two thus no labeling discussion took place. (See Transcript for Complete Discussion)*

d. Please discuss additional information that should be on the principal display panel to better inform consumers about the product.

Committee Discussion:
Committee recommendations for labeling included:
1. Listing the ingredients, medication strength and concentration on the front label.
2. Removing "Doctor Recommended", and all similar statements, from the front panel.
3. Removing pictures of infants/babies/ and children from the box.
4. Listing patients that should NOT take the product
5. Stating that individuals should not simultaneously take more than one product with the same ingredient(s)
(See Transcript for Complete Discussion)

e. Please discuss whether you believe the naming of the products contributes to consumer confusion.
(See Transcript for Complete Discussion)

5. Combination Products
Most cough and cold products are available as combination products. Combination products may be considered a problem because, for example, parents and caregivers may use several products not realizing that they are duplicating ingredients, and overdosing their children. Currently the monograph allows for combinations of several ingredients.

a. Should marketing of combination products be allowed for children (yes or no)? If no, for which age groups? In addressing this, please consider the following points:

- there may be advantages of combination products, assuming correct use
- there may be unintended consequences of prohibiting combination products in that parents will use multiple single ingredient products
- there may be disadvantages if overdosing occurs with multiple ingredients

If yes, should the number of active ingredients in combination products be limited in order to reduce the use of overlapping ingredients in different products (yes or no)?

Committee Discussion:
The committee proposed changing the wording of the question:

1. Assuming that these ingredients are proven safe and effective, should marketing for combination products be allowed for children between the ages of 2 to less than 6 years old for the common cold?
Yes: 14 **No: 4** **Abstain: 3**

2. Assuming that these ingredients are proven safe and effective, should marketing for combination products be allowed for children between the ages of 6 to less than 12 years old for the common cold?
Yes: 15 **No: 3** **Abstain: 3**

(See Transcript for Complete Discussion)

b. Discuss whether labeling changes or other approaches can improve the safety of combination products. If so, what would you recommend? When answering this question, consider whether all indications for each ingredient should appear on the label.
Committee Discussion:
The committee proposed changing the wording of the question:

Should label comprehension and actual use studies be done prior to allowing marketing of combination products?
Yes: 21 **No: 0** **Abstain: 0**

The committee further recommended that all combination products contain a warning that states "Do not take with other cough/cold products." (See Transcript for Complete Discussion)

The meeting was adjourned at approximately 4:00 p.m. on October 19, 2007.

These summary minutes for the October 18-19, 2007 Joint Meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee of the Food and Drug Administration were approved on October 31, 2007.

I certify that I attended the October 18-19, 2007, Joint Meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee of the Food and Drug Administration meeting and that these minutes accurately reflect what transpired.

/S/
Darrell Lyons, B.S.N
Designated Federal Officer

/S/
Mary Tinetti, M.D.
Chair, NDAC

/S/
Marsha D. Rappley, M.D.
Chair, PAC

Pulmonary Review

REFERENCE 1

"Anatomy and Physiology of the Nose and Control of Nasal Airflow," *Middleton's Allergy, Principles & Practice*, 6th ed. Philadelphia, 2003, Mosby, p 775-787

REFERENCE 2

"Acoustic Rhinometry in the Practice of Allergy," *Ann Allergy Asthma Immunol* 2006; 97:745-52.

REFERENCE 3

"Assessment of Nasal Cycle by Acoustic Rhinometry and Rhinomanometry," *Otolaryngol Head Neck Surg* 2003; 128:510-6.

REFERENCE 4

"Diagnosis and Management of Rhinitis: Complete Guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology," *Ann Allergy Asthma Immonul* 1998; 81:478-518.

3. Draft Guidance

Guidance for Industry

Allergic Rhinitis: Clinical Development Programs for Drug Products

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication of the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this draft guidance document are available from the Drug Information Branch, Division of Communications Management, HFD-210, 5600 Fishers Lane, Rockville, MD 20857, (Tel) 301-827-4573, or from the Internet at http://www.fda.gov/cder/guidance/index.htm.

For questions on the content of the draft document contact Martin H. Himmel, 301-827-1050.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
April 2000
Clin.

Guidance for Industry

Allergic Rhinitis: Clinical Development Programs for Drug Products

Additional copies are available from:

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5600 Fishers Lane
Rockville, Maryland 20857
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
April 2000
Clin.

Table of Contents

GUIDANCE FOR INDUSTRY[1]

(Due to the complexity of this draft document, please identify specific comments by line number. Use the pdf version of the document whenever possible.)

Allergic Rhinitis: Clinical Development Programs for Drug Products

I. INTRODUCTION

This guidance is intended to assist sponsors of new drug applications (NDAs) in designing development programs for oral and intranasal drug products for the treatment of allergic rhinitis in children and adults. The guidance addresses issues of study design, effectiveness, and safety for new drugs being developed for the treatment of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR).

II. BACKGROUND

Information about the pathophysiology and treatment of allergic rhinitis and its subtypes, SAR and PAR, has grown markedly in the past decade. The recommendations in this guidance are based on a careful assessment of important issues raised in the review of both adult and pediatric allergic rhinitis clinical trials and the Agency's current understanding of the mechanism of the two related disorders of SAR and PAR. The pathophysiology of SAR and PAR are very similar in terms of the chemical mediators produced and end-organ manifestations, with differences between the two entities primarily based on the causes and duration of disease. The study design issues pertaining to SAR and PAR trials are also very similar. Thus, these two categories are treated collectively in this guidance as *allergic rhinitis*, with differences in recommendations for the design of SAR and PAR trials indicated.

When finalized, this document will replace the previous *Points to Consider: Clinical Development Programs for New Nasal Spray Formulations* (January 1996). Sponsors are encouraged to discuss details of study design and specific issues relating to individual drug products with division review staff prior to conducting clinical trials.

Allergic rhinitis includes both nasal and non-nasal symptoms. The main nasal symptoms of allergic rhinitis are nasal itching (i.e., nasal pruritus), sneezing, rhinorrhea, and nasal congestion. Nasal pruritus and sneezing are induced by sensory nerve stimulation, whereas congestion

[1] This guidance has been prepared by the Division of Pulmonary and Allergy Drug Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on clinical trial design of seasonal and perennial allergic rhinitis studies in adults and children. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

results from vasodilation with resultant engorgement of cavernous sinusoids. Rhinorrhea can be induced by increased vascular permeability as well as direct glandular secretion. Important non-nasal symptoms commonly associated with allergic rhinitis include eye itching, eye tearing, itching of ears and/or palate, and eye redness.

A growing number of chemical mediators are believed to contribute to allergic rhinitis. They include histamine, leukotrienes (LTC_4, LTD_4, and LTE_4), kinins, prostaglandins, chemotactic factors, neuropeptides (e.g., substance P, CGRP, VIP), interleukins -1, -5, -6, -8, and tumor necrosis factor-α. Additional mediators with a potential role in allergic rhinitis will likely be identified in the future. Despite different causes and temporal patterns of disease, the same groups of chemical mediators appear to be regulators of the responses in seasonal and perennial allergic rhinitis. It is for this reason that distinctions between SAR and PAR in terms of clinical trial design will be made only in clinically relevant areas.

III. OVERALL CONSIDERATIONS - ADULT PROGRAM

A. New Molecular Entity

1. Number of Trials

For approval of a new molecular entity in adult and adolescent patients (age 12 years and older), at least two adequate and well-controlled phase 3 clinical trials are recommended to support either the SAR or PAR indication. Alternatively, a sponsor can submit one SAR and one PAR trial in support of both the indications, if both trials are adequate and well-controlled phase 3 trials and both trials demonstrate the safety and effectiveness of the drug for the indications.

2. Dose

The dose-response relationship for the new drug should be evaluated in these trials. These trials, or other supporting trials, should identify a *lowest effective dose* for the drug (i.e., the lowest dose that demonstrates a statistically significant difference between the to-be-marketed drug and the placebo). This recommendation is particularly important for intranasal corticosteroids.

3. Safety Monitoring

These trials should also address safety concerns, such as monitoring for adverse events, performing routine laboratory tests (i.e., blood chemistry, liver function tests, complete blood count with differential), urinalyses, and electrocardiograms, as appropriate. For SAR and PAR phase 3 trials, routine laboratory tests should be obtained in study patients at least at the initial screening and at the last visit.

For some allergic rhinitis drugs (particularly drugs in the antihistamine class), part of the safety program should include a thorough cardiac safety evaluation, with studies performed in both men and women. A suggested approach would include:

- Screening and end-of-treatment ECGs, including a careful assessment of the QT_c interval and any T wave abnormalities, as read by a ECG reviewer blinded to study treatment.

- Human dose escalation studies that evaluate serial ECGs at drug exposures up to dose-limiting toxicity of any organ system.

- For drugs metabolized by the cytochrome P450 3A4 system, drug interaction studies performed with both a macrolide and azole antibiotic.

- 24-hour Holter monitoring performed before, during, and, as appropriate, on completion of the efficacy trials for allergic rhinitis drugs suspected to have an effect on QT_c intervals from previous studies.

In addition to the studies described above, case report forms and study reports should include a detailed description of all serious cardiac adverse events and pertinent ECGs.

Sponsors are encouraged to contact the review division regarding appropriate cardiac safety monitoring for their respective drug development programs.

For many allergic rhinitis drugs, some assessment of the degree of sedation compared to the placebo should be provided in the safety database. This should primarily be based on individual patient adverse event reports of sedation and/or drowsiness (or similar terminology, as defined by the sponsor's adverse event dictionary).

Generally, long-term safety data should include at least 300 patients evaluated for 6 months and 100 patients evaluated for 1 year. The overall patient database should include at least 1500 patients. (See the International Conference on Harmonisation guidance on the *Extent of Population Exposure Required to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-Life Threatening Conditions* (March 1995).)

4. Corticosteroid Issues

Important safety issues for intranasal corticosteroids that would ordinarily be addressed in the adult clinical program include:

- Assessment of adrenal function using either timed urinary free cortisol level measurements (i.e., 12-hour or 24-hour), or 24-hour plasma cortisol AUC levels pretreatment and after at least 6 weeks post-treatment with study medication. A placebo and an active control (e.g., oral prednisone) should be included in these studies.

- Evaluation for possible cataract formation by slit-lamp examination, pre- and post-treatment.

- Evaluation for glaucoma, using intra-ocular pressures monitored pre- and post-treatment.

B. Change in Formulation and/or Device

1. Oral Formulations

For a change in an oral dosage form from an approved oral formulation to a new oral formulation of the same drug substance, an alternative to conducting the new molecular entity program described above is to demonstrate bioequivalence between the two formulations. This is based on pharmacokinetic comparisons (e.g., AUC, C_{max}, C_{min}) between the approved and to-be-marketed formulations. This equivalence approach allows the indications and patient populations for the new formulation to be the same as those described in the labeling of the approved product. If a significant new excipient, not previously administered at comparable levels to humans, is present in the new formulation, or if the tolerability of the new formulation is otherwise in question, short- and possibly long-term safety data may still be important for patients receiving the new formulation, even if bioequivalence is demonstrated. Additional safety and efficacy trials may be necessary to support a new formulation if bioequivalence is not demonstrated.

2. Topical Nasal Formulations

For changes in formulation and/or device for a topical nasal product (e.g., aqueous pump, spray), one of two approaches can be used to demonstrate the safety and effectiveness of the new drug product: (1) establishment of comparability between the new and previously approved (reference) formulation, or (2) development of the new formulation and/or device by a usual program for a new drug product (i.e., *stand-alone approach*).

- Comparability Approach

To demonstrate clinical comparability between the new and reference formulations, comparison of the dose-response curves of these two formulations in a single

efficacy and safety trial is recommended. Two doses of each formulation, in addition to placebo, are desirable for dose-ranging determination. The dose-ranging study should be designed to permit determination of how doses of the new formulation compare to the approved doses of the reference formulation with regard to onset of action and effectiveness. Comparative pharmacokinetic (PK) measurements (C_{max}, T_{max}, and AUC) should be included in this trial, as appropriate and technically feasible. If the reference formulation is indicated for both SAR and PAR, the dose-ranging trial can be performed in patients with either SAR or PAR (see section V of this guidance, Protocol Issues and Elements, for recommended trial durations). If the reference formulation is approved for indications in addition to SAR and/or PAR (e.g., nasal polyps or nonallergic rhinitis) no additional studies are needed to support the same indications for the new product, if comparability, as described above, is well established between the new and reference formulation.

- Stand-Alone Approach

An alternative approach or *stand-alone approach* for evaluating a topical nasal drug product with a formulation change could be a single, dose-ranging, placebo-controlled efficacy and safety trial of the new formulation in patients with either SAR or PAR. A single dose of the reference formulation as a positive control is recommended. Demonstration of effectiveness for either of these two clinical indications would allow labeling to include efficacy for both, if the reference formulation already had labeling for both. If additional indications (e.g., nasal polyps and nonallergic rhinitis) previously approved for the reference formulation are sought for the new formulation, a single clinical trial for each additional indication is recommended. Furthermore, as with the *comparability approach*, determination of the pharmacokinetics of the drug is recommended during the stand-alone approach and can be performed during the efficacy trial, if feasible.

3. Safety Monitoring

For both oral and topical nasal formulation programs described above, safety monitoring should be included for the duration of the trials. This would include evaluation of adverse clinical events, routine laboratory tests (i.e., blood chemistry, liver function, complete blood count with differential), urinalysis, and ECGs, as appropriate.

In either of these formulation programs, demonstration of long-term safety may still be important, if new inactive ingredients have been added that could affect safety, or if the new formulation and/or device results in higher systemic exposure to active ingredients compared to the approved product. In addition, if pharmacokinetic data for the formulations are not feasible, long-term safety data for the new formulation may be recommended. If necessary, long-term safety may be established by

documenting exposure of at least 200 patients to the new formulation for 6 months at the dosage proposed for marketing. Due to the duration, these studies are generally conducted in patients with PAR. An active control arm, consisting of a single dosage level of the reference formulation, is recommended. Symptom-guided dosage adjustment by study patients during the long-term open label study should be avoided, as this complicates analysis of the safety data. To minimize dropouts and to address ethical considerations, stratification of patients and dosage according to symptom severity is acceptable at the start of the open label study. However, a sufficient number of patients who receive the highest dose proposed for marketing should be included. Rescue medication should not include other intranasal drugs or intranasal products.

4. Corticosteroid Issues

For corticosteroids, if the new formulation causes higher systemic exposure to the drug substance than other formulations (either intranasally or orally inhaled) already marketed or under development for which an adequate assessment of HPA axis effects has been conducted, or if pharmacokinetic data on these other formulations is unavailable, an evaluation of the effect of the new formulation on the HPA axis is strongly recommended. For HPA axis evaluation, measurement of timed (12- or 24-hour) urinary free cortisol levels or serum cortisol AUC before and after 6 weeks of treatment are the preferable methods of assessment. If the sponsor plans to claim comparability between the reference and new formulations, and a pharmacokinetic comparison of the two products is not available, comparison with the highest marketed dose of the reference formulation is recommended.

For a change in a device, data on the performance and reliability of the new device over the period of intended use may need to be provided.

IV. OVERALL CONSIDERATIONS - PEDIATRIC PROGRAM

A. New Molecular Entity or New Pediatric Indication

The pediatric age ranges proposed for a drug product, particularly for very young patients, should be justified by the sponsor based on the presence of disease and the need for treatment in that age group. Drugs indicated for the treatment of allergic rhinitis are used in children below the age of 2 years; therefore, a complete pediatric program should evaluate the safety of antihistamines in children down to age 6 months. Similarly, based on clinical use experience, the safety of intranasal corticosteroids, cromolyn-like drugs, and anticholinergics should be evaluated in children down to age 2. Sponsors are encouraged to discuss the specifics of pediatric programs with the division on a case-by-case basis.

1. Drugs Not Previously Studied in Adults

For approval of a new molecular entity in pediatric patients (patients younger than 12 years), the number of studies recommended depends on whether the drug is already approved in adult patients. For a new molecular entity (NME) not previously approved or adequately studied in adults, the clinical program would be the same as that described for adults. This would include two adequate and well-controlled safety and efficacy trials along with appropriate long- and short-term safety data. For an NME intranasal corticosteroid, the performance of a growth study (possibly postapproval) is recommended in order to assess the potential of the corticosteroid to suppress growth in children.

2. Drugs Already Studied in Adults

For drugs already approved and/or adequately studied in adults but not yet studied in children, an appropriate pediatric dose should be determined. In addition, adequate short- and long-term safety information for the proposed pediatric age group should be provided. For oral formulations where a reasonable pharmacokinetic/pharmacodynamic (PK/PD) link for effectiveness has been established, PK data from children can be used to determine comparable exposure to adult patients, and therefore the appropriate pediatric dose.

For intranasal formulations, the performance of efficacy studies in pediatric patients is recommended, since plasma drug levels are not consistently detectable or reliable as measures of local bioavailability and topical efficacy.

3. Safety Data

Typically, 3 months of additional specific pediatric safety data for intranasal products and 1 month of additional safety data for oral products are recommended. These data should be collected in placebo controlled trials. However, the duration and number of pediatric patients exposed to the study drug for safety monitoring should be determined on an individual basis for each drug, based on anticipated side effects, pediatric PK data, and safety concerns.

4. Corticosteroid Issues

For intranasal corticosteroids, performance of a 6-week HPA axis study is recommended. Because of ethical concerns about the use of oral prednisone as an active comparator in adrenal response studies in children, inclusion of an oral prednisone arm in pediatric adrenal assessment studies is not typically recommended. However, inclusion of an active comparator arm (e.g., an intranasal corticosteroid approved in the pediatric population) is encouraged.

Based on recent information that intranasal corticosteroids have the potential to decrease growth velocity in children, a growth study is recommended for prepubertal children as a phase 4 commitment, if not before. If the studies are to be performed postapproval, it may be useful for a sponsor to include a knemometry study in the NDA submission to provide some PD growth data for consideration during the initial review. Growth studies should evaluate growth before and after treatment with the intranasal corticosteroid, using stadiometry to assess growth. Such a growth study should enroll patients with allergic rhinitis, incorporate a run-in period, and be placebo controlled. Sponsors should ensure that an adequate sample size is studied and that there is a reasonable duration of treatment (ordinarily 1 year). These recommendations allow for a better estimate of the decrease in growth velocity seen in association with intranasal corticosteroid use. Information on a clinically significant change in growth derived from knemometry studies should not be used to determine the expected change in growth velocity for longer-term studies that use stadiometry to measure growth. This is because of the nonlinearity of growth and differences in study durations for these two techniques. Sponsors are encouraged to discuss the details of their pediatric growth study design with the review division.

B. Change in Formulation and/or Device

In situations where a sponsor has conducted a change in the formulation and/or device comparability program in adults, as described above, additional pediatric efficacy studies may not be required if:

- The safety, efficacy, and PK of the new formulation are comparable to that of the reference formulation in adults, and

- The reference formulation has been approved for use in an appropriate pediatric age range.

However, depending on the specific changes that were made in the formulation and/or device, additional safety and/or use studies in children may be needed.

V. PROTOCOL ISSUES AND ELEMENTS

A. Trial Design

In the development programs of allergic rhinitis drugs, otherwise well-designed and well-conducted studies may occasionally fail to show effectiveness. This is due in part to the subjective nature of the assessments and spontaneous variability in the disease. This observation makes the use of a placebo control of paramount importance, since a

positive-control equivalence trial cannot be interpreted in such a situation. If the intent is to show that the new product is significantly more effective than an approved active control, a positive-control study may be sufficient.

The following are general recommendations on trial design for phase 3 allergic rhinitis (SAR and PAR) trials in adults and adolescents (older than 12 years) and children (younger than 12 years).

- These studies should be double-blind, placebo-controlled, and parallel group, preferably with a placebo run-in period.

- Inclusion of an active control arm is recommended for both reformulation programs (as described above) and for new drug development programs. For the new drug development program, the positive-control study is helpful in interpreting trials in which there is not a demonstrable difference between the test drug and the placebo.

- The duration of the double-blind treatment period should be at least 2 weeks for SAR trials and 4 weeks for PAR trials.

- For SAR trials, the study protocol should discuss plans for measuring pollen counts at the different study centers. The study report should document the exposure of patients to the relevant allergens during the study period. It may also be helpful to collect data on the number of rainy days during the trial and the extent of patient exposure to outdoor air.

- For SAR trials, randomization of patients within each center into the double-blind portion over a short time period (e.g., 3-4 days) is encouraged, as this generally reduces variability in allergen exposure.

- Many patients with PAR may have concomitant SAR. Therefore, PAR trials should be conducted during a time when relevant seasonal allergens are less abundant and therefore less likely to influence results of the trial (i.e., late fall and winter).

B. Inclusion Criteria

- For SAR effectiveness trials, patients should have a history of SAR for a minimum of 2 years before study entry. Documentation of sensitivity by positive skin testing (by prick or intradermal methods) or by adequately validated in vitro tests for specific IgE (e.g., RAST, PRIST) to the relevant seasonal allergen for the geographic area of the study within 12 months prior to enrollment is recommended. A positive skin test is generally defined as a wheal ≥ 3 mm larger than the diluent control for prick testing or ≥ 7 mm larger than the diluent control for intradermal

testing. Positive in vitro tests are determined by the standards of the individual reference laboratory.

- For PAR effectiveness trials, allergy to perennial allergens (e.g., dust mites, cockroaches, cats, dogs, molds) should be demonstrated in study patients by prick or intradermal skin testing (using the criteria for positivity above) or by adequately validated in vitro tests for specific IgE (e.g., RAST, PRIST). These tests should be done during the 12 months before enrollment. The patient should have a relevant allergy history to the tested allergen.

- For approximately 1 month preceding enrollment in the study, patients should not start immunotherapy or have a change in dose, and they should maintain the same dose throughout the trial.

Patients enrolled in treatment studies (as opposed to prophylaxis studies) should be experiencing symptoms meeting or exceeding an appropriate minimum level at the time of study enrollment. This could be ensured by assessing the severity of the symptoms for the primary endpoint and requiring at least moderate severity for all or the majority of individual symptoms, as defined by the study's symptom scoring scale.

C. Exclusion Criteria

The following conditions should exclude possible study participants:

- Asthma, with the exception of mild intermittent asthma (see the 1997 NAEPP guideline on asthma severity criteria), to lessen confounding by asthma medications

- Chronic or intermittent use of inhaled, oral, intramuscular, intravenous, and/or potent or super-potent topical corticosteroids

- Use of long-acting antihistamines

- Prohibited medications or inadequate washout periods (for certain classes of medications). The following washout periods are generally sufficient:

  Intranasal or systemic corticosteroids (1 month)
  Intranasal cromolyn (2 weeks)
  Intranasal or systemic decongestants (3 days)
  Intranasal or systemic antihistamines (3 days)
  Loratadine (10 days).

- Documented evidence of acute or significant chronic sinusitis, as determined by the individual investigator

- Chronic use of concomitant medications (e.g., tricyclic antidepressants) that would affect assessment of the effectiveness of the study medication

- A history of hypersensitivity to the study drug or its excipients

- Rhinitis medicamentosa

- Presence of ocular herpes simplex or cataracts (for intranasal corticosteroid trials), or a history of glaucoma (for intranasal corticosteroid or anticholinergic trials)

- Planned travel outside the study area for a substantial portion of the study period by potential participants

D. Blinding

Because allergic rhinitis trials are based on subjective endpoints, blinding is a critical consideration. Blinding to study medication should be carefully described in the study protocol (i.e., description of how the product is masked). If double-blinding is not possible, a rationale for this should be provided, along with a discussion of the means for reducing or eliminating bias. For nasal inhalers or pumps, a description of differences in appearance between active and placebo treatments should be provided in the protocol (e.g., differences in the device or in the odor or characteristic of the formulation) to help determine the adequacy of the study blind.

E. Formulations and Dosage Regimens

For all classes of allergic rhinitis drugs, sponsors are encouraged to provide information in the clinical study protocol on the specific formulations used for both the to-be-marketed drug and the placebo, along with a description of the dosing regimen. The study report should discuss whether the studied formulation was the to-be-marketed product, and if not, how the safety and effectiveness of the studied formulation will be bridged to the to-be-marketed formulation. If *bridging* of one formulation to another is proposed, information about the formulation composition and study lots should be included in the study reports for the respective products.

F. Evaluation

1. Assessment of Patient Compliance

Information about how compliance with medication use will be determined and documented throughout the trial and how noncompliance and/or missing data will be dealt with, either in the form of patient exclusion or exclusion of data points (e.g., use of

last visit data carried forward) should to be provided in the study protocol and the study report.

2. Assessment of Rescue Medication Use

If rescue medications are allowed during the study, documentation should be provided in the study protocol on how rescue medication use will be analyzed in the different treatment groups. In the clinical trial report, a section presenting rescue medication use in the different study medication groups should be provided.

3. Rating System

The preferred measures of effectiveness in allergic rhinitis trials are patient self-rated *instantaneous* and *reflective* composite symptom scores. These summed scores generally include the following four nasal symptoms: rhinorrhea, nasal congestion, nasal itching, and sneezing, rated on a 0-3 scale of severity. Addition of non-nasal symptoms to the composite score might be pertinent for certain drug products, such as systemically active antihistamines, and should be discussed with the division on a case-by-case basis. Exclusion of symptoms from the composite score may be allowable, based on the drug's mechanism of action (e.g., exclusion of nasal congestion for antihistamines). While both patient self-rated symptom scores and physician-rated scores can be measured, the patient-rated scores are preferred as the primary measure of effectiveness.

A common allergic rhinitis rating system that has been used in clinical trials is the following 0-3 scale:

- 0 = absent symptoms (no sign/symptom evident)
- 1 = mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated)
- 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable)
- 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping)

Regardless of the scoring system chosen, a detailed description of the symptom rating scale should be provided to patients. This should include instructions on proper completion of the symptom diary and definitions of the different categories in the scale.

4. Recording Scores

Patients should record scores in a diary at least as often as the daily dosing interval. Collection of both *reflective* symptom scores (i.e., an evaluation of symptom severity

after a predefined time period such as 12 hours) and *instantaneous* symptom scores (i.e., an evaluation of symptom severity immediately before the next dose) is recommended. Reflective symptom scores assess the overall degree of effectiveness over a prespecified time interval, whereas instantaneous scores assess effectiveness at the end-of-dosing interval.

VI. DATA ANALYSIS ISSUES

A. Collection of Data

Symptom scores should be collected at baseline and daily over the course of the trial. Collection of baseline symptom scores over several days immediately preceding patient randomization will permit the evaluation of baseline comparability of the various treatment arms, as well as the determination of treatment effects over time.

An appropriate primary efficacy endpoint is the change from baseline in the total nasal symptom score (TNSS) for the *entire* double-blind treatment period (2 weeks for SAR and 4 weeks for PAR). Depending on the drug class being evaluated, the TNSS is defined as a composite score of at least three of the following four nasal symptoms: rhinorrhea, nasal congestion, nasal itching, and sneezing. Inclusion of nasal congestion in the TNSS may be appropriate for an intranasal corticosteroid or a decongestant, but may not be for an antihistamine, anticholinergic, or cromolyn-like agent.

When designing allergic rhinitis protocols, sponsors are encouraged to provide the value of a clinically meaningful change in the primary efficacy endpoint and the basis for this value. The statistical section of the protocol should also discuss powering of the trial based on this relevant change.

In addition to evaluating the effectiveness of the drug over the entire double-blind period, additional data presentations are helpful in evaluating the effectiveness of the drug. These include:

- Presenting the a.m. and p.m. symptom scores separately for both the reflective and instantaneous symptom assessments.

- Presenting effectiveness data for the first few days of the trial separately for both the reflective and instantaneous symptom assessments. This data presentation should also separate the a.m. and p.m. scores. This allows some assessment of the onset of action.

- Presenting the efficacy data for each week individually for both the reflective and instantaneous symptom assessments. This allows determination of both the onset of action and the durability of the response over the course of the clinical trial.

Additional secondary efficacy analyses may include the individual patient-rated symptoms that comprise the total symptom complex for the reflective and instantaneous symptom assessments for both a.m. and p.m. In addition, other patient-rated symptoms and all physician-rated symptoms can be included as secondary efficacy endpoints.

B. Time to Maximal Effect

The time to maximal effect for an allergic rhinitis medication is the earliest time (days, weeks) that the primary efficacy endpoint demonstrates the greatest numerical difference from the placebo in change from baseline. Sponsors are encouraged to include frequent symptom measurements to determine when patients may expect to see the greatest benefit from use of the drug.

C. Duration of Effect (End-of-Dosing Interval Analysis)

Evaluation of the duration of effect, as measured by instantaneous symptom scores at the end of the dosing interval, is highly encouraged to assess the appropriateness of the dosing interval. A sponsor should demonstrate, as part of the drug development program, a significant difference between drug and placebo at the end of the dosing interval.

D. Onset of Action

The definition of the onset of action of an allergic rhinitis drug is the point at which patients might reasonably expect to see a meaningful decrease in their allergic rhinitis symptoms. Statistically, it is the first time point after initiation of treatment when the drug demonstrates a change greater than the placebo treatment from baseline in the primary efficacy endpoint. This statistically significant difference between drug and placebo should be maintained for some period from this point onward.

Because onset of action information in labeling may be used as a superiority claim, at least two studies are recommended to support a particular onset of action claim. (It is useful to assess onset of action during development, regardless of any proposed claims). The two trials do not have to be identical in design, nor do they have to evaluate both SAR and PAR. Since onset of action is in large part a pharmacodynamic issue, a number of different study types could be used. Following are three study types that have been used.

- Standard phase 3 allergic rhinitis efficacy trials in which symptom scoring data are collected frequently for the first few days

- A single-dose, parallel group, placebo-controlled study of patients in a *park setting* in which patients are exposed to relevant outdoor seasonal allergens and, following dosing, have nasal symptoms evaluated on an hourly basis

- An inhalation chamber study (also known as environmental exposure unit or EEU) in which previously asymptomatic patients are exposed to a relevant allergen (generally a seasonal allergen, such as ragweed) in a controlled indoor setting and, following dosing, have their nasal symptoms evaluated on an hourly basis

Onset of action data can come from any of these three study types. However, if EEU and/or park studies are used to support an onset of action claim shorter than the onset of action seen in the phase 3 trials, these results should be replicated. This is due to the shorter duration of these trials and the restricted setting and manner in which they are conducted. In any case, information about onset of action derived from the phase 3 trials used to support approval should be included in the proposed package insert along with any data from park or chamber studies, to reflect the real world setting of the treatment trials.

VII. SAR PROPHYLAXIS TRIALS

Many variables should be considered in designing adequate prophylaxis trials for seasonal allergic rhinitis. Some of the issues that should be considered include:

- The recruitment of patients who are asymptomatic or have only mild rhinitis symptoms at baseline

- The optimal duration of pretreatment with study drug

- The difficulty in capturing the peak of the allergy season or a time when pollen counts are at their highest

- The advantages of pretreatment and/or prophylactic therapy versus treatment at the time of symptoms

Sponsors who choose to conduct prophylaxis studies should propose a minimum duration of drug exposure prior to anticipated allergen exposure and should carefully discuss the study design for each drug product with the division before initiating such studies.

Performance of an EEU study may address the adequate prophylaxis period for a seasonal allergen. However, a prophylaxis claim should be based in part on standard allergic rhinitis trial settings.