## DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

### Food and Drug Administration

### [ 21 CFR Parts 338, 339, 340 ]

[Docket No. 75–N–0244]

### OVER-THE-COUNTER DRUGS

### Proposal To Establish Monographs for OTC Nighttime Sleep-Aid, Daytime Sedative, and Stimulant Products

Pursuant to Part 330 (21 CFR Part 330), the Commissioner of Food and Drugs received on October 21, 1975 the report of the Advisory Review Panel on Over-The-Counter (OTC) Sedative, Tranquilizer and Sleep-Aid Drug Products. In accordance with § 330.10(a)(6), the Commissioner is issuing (1) a proposed regulation containing the monographs recommended by the Panel establishing conditions under which OTC nighttime sleep-aid, daytime sedative and stimulant drugs are generally recognized as safe and effective and not misbranded, (2) a statement of the conditions excluded from the monographs 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 monographs 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 this Panel represents their best scientific judgment. It has been prepared independently of the Food and Drug Administration and does not necessarily reflect the Agency position on any particular matter contained therein. After a careful review of this document and all comments submitted in response to it, the Commissioner will prepare a tentative final regulation to establish monographs for OTC nighttime sleep-aid, daytime sedative and stimulant drug products. Comments on this document are due on or before March 8, 1976.

In accordance with § 330.10a()(2), all data and information concerning OTC sedative, tranquilizer, sleep-aid and stimulant drug products submitted for consideration by the Advisory Review Panel have been handled as confidential by the Panel and the Food and Drug Administration. 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 January 7, 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 the Food and Drug Administration, 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 monographs (Category I) be effective 30 days after the date of publication of the final monographs in the FEDERAL REGISTER.

2. That the conditions excluded from the monographs 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 monographs in the FEDERAL REGISTER, regardless whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monographs on the basis of the Panel's determination that the available data are insufficient to classify such conditions either as generally recognized as safe and effective and not misbranded or as not being generally recognized as safe and effective or would result in misbranding (Category III) be permitted to remain in use for 3 years after the date of publication of the final monographs 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.

In the following document, the Sedative, Sleep-Aid and Tranquilizer Panel set forth a concept known as "Category III with a marketing hold" (Category III (MH)) for doxylamine succinate and phenyltoloxamine dihydrogen citrate for use as OTC nighttime sleep-aids. The Panel concluded that these ingredients may be effective but require further testing. Since the ingredients have never before been marketed over-the-counter (OTC) as nighttime sleep-aids, the Panel concluded that there should be a marketing hold for that indication until adequate safety and effectiveness data are available. The Panel stated in their report that they were aware the effect of such a recommendation might cause the Food and Drug Administration to classify these ingredients in Category II and therefore, prohibit OTC marketing until an approved New Drug Application (NDA) is obtained by a drug manufacturer or until the OTC nighttime sleep-aid monograph (Part 338) is amended to include these ingredients.

The Panel in their recommendations also classified the ingredient diphenhydramine hydrochloride as an OTC nighttime sleep-aid as Category III but suggested marketing of this ingredient be permitted while final testing was carried out. This ingredient is presently a new drug marketed under an approved New Drug Application for prescription use only for several indications. Based on a review of this drug by the National Academy of Sciences—National Research Council (NAS/NRC), it was classified as "probably effective" for intractable insomnia. Diphenhydramine has never been legally marketed for any indication for over-the-counter use. The Panel raised questions regarding the safety and effectiveness of diphenhydramine as a nighttime sleep-aid which require resolution prior to classification of the ingredient in Category I.

The Commissioner has determined that an active ingredient classified as Category III which heretofore has been limited to prescription use or classified for OTC use at a dosage level higher than that available in an OTC drug product on December 4, 1975, as published in the FEDERAL REGISTER of December 4, 1975 (40 FR 56675), may not be lawfully marketed for OTC use until the tests and studies to satisfy the questions raised by the Panel have been conducted and the drug has been determined by the Food and Drug Administration to be generally recognized as safe and effective and not misbranded for over-the-counter marketing and so indicated in an appropriate monograph published in the FEDERAL REGISTER or a New Drug Application is approved. The Commissioner also concludes that the procedures promulgated in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464) establishing the OTC drug review do not provide for a "marketing hold" for Category III conditions and that such a concept is equivalent to classifying an ingredient in Category II. The classification by a Panel of an ingredient, historically a prescription ingredient, in Category III with or without a marketing hold represents no more than an opinion that the prescription ingredient may be shown at some future time to be generally recognized as safe and effective for OTC marketing with adequate studies.

Accordingly, the Commissioner reaches the immediate determination that doxylamine succinate, phenyltoloxamine dihydrogen citrate and diphenhydramine hydrochloride as OTC nighttime sleep-aids are new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)), implemented by § 310.3(g) and (h)(5) (21 CFR 310.3(g) and (h)(5)). Therefore, they cannot now be marketed over-the-counter for use as OTC nighttime sleep-aids. Prior to marketing OTC for such an indication, an approved New Drug Application is required or a determination must be made that the ingredients are generally recognized as safe and effective in a monograph.

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 considerations. Therefore, the Commissioner has proposed in the FEDERAL REGISTER of December 4, 1975 (40 FR 56675) to establish a policy to clarify the marketing status of all ingredients currently restricted to prescription use which an OTC Advisory Panel recommends as either Category I (safe and effective), Category II (not safe and effective) or Category III (the available data are insufficient to classify the drug) and also the use of active ingredients at dosage levels higher than that available in any OTC drug product on December 4, 1975 as published in the FEDERAL REGISTER of December 4, 1975 (40 FR 56675).

The Commissioner is aware of some concern about the safety of OTC nighttime sleep-aids in general and about diphenhydramine in particular due to possible hazards of misuse, abuse or other adverse societal impact. He is therefore, seeking public comment on these issues at this time. The Panel addressed these issues to some degree by recommending a product container size limitation to avoid abuse. However, the Commissioner believes the broader safety issue of possible misuse and societal impact of OTC nighttime sleep-aids should be publicly reviewed through comment upon this proposal.

The conclusions and recommendations contained in the report of the Advisory Review Panel on OTC Sedative, Tranquilizer and Sleep-Aid products to the Commissioner are as follows:

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, which were made effective immediately. Pursuant to these regulations the Commissioner issued a request for data and information on all sedative, tranquilizer and sleep-aid active ingredients in drug products, in the FEDERAL REGISTER of August 22, 1972 (37 FR 16885). The Commissioner issued in the FEDERAL REGISTER of May 25, 1973 (38 FR 13763) an additional request for data and information on all stimulant ingredients.

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 products containing sedative, tranquilizer, sleep-aid and stimulant ingredients:

Karl Rickels, M.D., Chairman, Calton K. Erickson, Ph.D., Helen Dunn Gouin, R.Ph., M.S., Ernest L. Hartmann, M.D., Sumner M. Kalman, M.D., Lester C. Mark, M.D., Frances S. Norris, M.D.

The Panel was first convened on November 15, 1972 in an organizational meeting. Working meetings were held on January 29 and 30, April 19 and 20, June 25 and 26, September 17 and 18, November 5 and 6, December 17 and 18, 1973; February 4 and 5, March 1 and 2, April 1 and 2, July 9 and 10, October 28 and 29, 1974; January 27 and 28, March 3 and 4, April 28 and 29, August 14 and 15, September 29 and 30, 1975.

The Panel included the following nonvoting liaison representatives: Ms. Renee Butler, nominated by an ad hoc group of consumer organizations. Joseph L. Kanig, Ph.D., and in his absence Mr. Peter G. Neaman or Mr. Max Richburg, R.Ph., were nominated by the Proprietary Association. Harvey I. Chernov, Ph.D., an employee of the Food and Drug Administration served as Executive Secretary until September 1973 when he was succeeded by Irma Hobart, M.D., also an employee of the Food and Drug Administration. Others who served with the Panel were Michael Kennedy, Panel Administrator, Melvin Lessing, M.S., R.Ph., Drug Information Analyst and George H. Kerner, Consumer Safety Officer.

In addition to the Panel members and liaison representatives, the Panel utilized the advice of the following consultant:

Robert W. Downing, Ph.D.

In addition, the following individuals provided useful scientific information by correspondence at the request of the Panel which is included in the administrative record:

Jerome W. Bettman, M.D., Nelson Irey, M.D., Irving J. Selikoff, M.D.

The following individuals were given an opportunity to appear before the Panel to express their views, either at their own request or at the Panel's request:

Clinton C. Brown, M.D., Robert B. Choate, Leonide Goldstein, M.D., Andrew Graham, Esq., Martin Himmel, Anita Johnson, Esq., Ben Marr Lanman, M.D., Leslie M. Lueck, Ph.D., Joseph Pittelli, M.D., E. Ned Schultz, M.D., Roger A. Schultz, Esq., Robert A. Sperber, M.D., Garrett W. Swenson, Esq., Gerald W. Vogel, 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 September 29, 1975 in arriving at its conclusions and recommendations.

The Panel first attempted to define the terms currently used in OTC products to be sure that these terms were clear to the consumer. The Panel was unable to define the term "tranquilizer" in relation to drugs for OTC daytime sedation. The Panel believes that the term "tranquilizer" is inappropriate for an OTC product because to the consumer, the term "tranquilizer" is misleading. The term promises a quantitatively different effect than that which an OTC drug is able to provide. Tranquilizer is a term properly identified with a medically prescribed psychotropic drug which is available by prescription and should in fact only be available by that source. For this reason, the Panel adopted the use of the term "daytime sedative." It was also apparent to the Panel that it would be necessary to appropriately define a product used to induce sleep at night. Such a product with the term "sedative" or "sleep-aid" did not in the Panel's estimation provide sufficient guidance to the consumer as to the use of the product. Therefore, the Panel is recommending to the Commissioner that the term "nighttime sleep-aid" be adopted for use of a product that will induce sleep.

These two terms "daytime sedative" and "nighttime sleep-aid" are descriptive of the types of products presently used as OTC medications. They indicate the time of use and the effect that the consumer will realize without causing confusion or misunderstanding. Henceforth, in this document, the Panel has adopted and uses the terms "daytime sedative" and "nighttime sleep-aid."

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:

I. Conditions under which nighttime sleep-aid, daytime sedative and stimulant products are generally recognized as safe and effective and are not misbranded.

II. Conditions under which nighttime sleep-aid, daytime sedative and stimulant products are not generally recognized as safe and effective or are misbranded.

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

The Panel recommends the following for each category of drugs:

1. That the monographs (Category I) be effective 30 days after the date of publication of the final monographs in the FEDERAL REGISTER.

2. That the conditions excluded from the monographs 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 monographs in the FEDERAL REGISTER, regardless whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monographs (Category III) on the basis of the Panel's determination that the available data are insufficient 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 3 years after the date of publication of the final monographs 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 provided a period of 3 years for testing Category III antihistamines as nighttime sleep-aids and be-

lieves that this period of time is necessary because testing facilities are limited. For example, only a few electroencephalograph (EEG) sleep laboratories exist and few experienced investigators are available to perform such studies. Much of the current effort is being utilized in studies on newer prescription drugs. Thus, to shortcut the practical time it would take to carry out these studies in a reasonable manner would not be in the best interest of the consumer, the industry or the testing laboratories. The Panel is aware that it generally takes considerable time to design, set up, conduct, analyze and report these tests. The Panel considers that the Category III ingredients (antihistamines) being reviewed are basically safe as OTC nighttime sleep-aid products. Their safety is therefore not in serious question unless higher dosages than recommended by the Panel as OTC nighttime sleep-aids are used. Thus the question of approval of these preparations is based upon demonstration of effectiveness.

The Panel also during its review realized that two antihistamines are not marketed as OTC sleep-aids but are available for other OTC indications, e.g., antitussive (cough suppressant) or as a calmative, at dosage levels lower than that which would be necessary to produce a sedative effect. These ingredients could possibly be used as OTC nighttime sleep-aids but the Panel is concerned with allowing marketing until further data are obtained on their safety and effectiveness. Therefore, the Panel created a Category III–MH (marketing hold) designation with a request that no marketing as an OTC nighttime sleep-aid be allowed until further testing has been done. These ingredients are discussed below. (See paragraph II C 3 below—*Conditions under which the available data are insufficient to permit final classification at this time.*)

## I. Submission of Data and Information

### A. Request for Submission of Sedative, Tranquilizer and Sleep-Aid Drug Data

Pursuant to the notice published in the Federal Register of August 22, 1972 (37 FR 16885) requesting the submission of data and information on sedative, tranquilizer, and sleep-aid drugs, the following firms made submissions relating to the indicated products:

1. *Submissions by firms.*

| *Firm* | *Marketed Products* |
|---|---|
| Block Drug Co., Inc., Jersey City, NJ 07016. | Nytol Capsules, Nytol Tablets. |
| Bristol-Myers Co., New York, NY 10022. | Excedrin P.M. Tablets. |
| Endo Laboratories, Inc., Garden City, NY 11530. | Dilone Tablets, Percogesic Tablets. |
| Jeffrey Martin, Inc., Union, NJ 07083. | Compoz Tablets. |
| Miles Laboratories, Inc., Elkhart, IN 46514. | Miles Nervine Capsules, Miles Nervine Liquid, Miles Nervine Tablets. |
| Whitehall Laboratories, Inc., New York, NY 10017. | Quiet World Tablets, Sleep-Eze Tablets. |
| J. B. Williams Co., Inc., Cranford, NJ 07016. | Sominex Capsules, Sominex Tablets. |

In addition, the following firms made related submissions:

| *Firm* | *Submissions* |
|---|---|
| Johnson and Johnson Co., New Brunswick, NJ 08903. | Talc. |
| Miles Laboratories, Inc., Elkhart, IN 47514. | Diphenhydramine hydrochloride. |
| Monsanto Industrial Chemicals Co., St. Louis, MO 63166. | Methapyrilene fumarate, Methapyrilene hydrochloride. |
| Parke, Davis & Co., Ann Arbor, MI 48106. | Diphenhydramine hydrochloride. |
| Pfizer Inc., New York, NY 10017. | Doxylamine succinate. |
| J. B. Williams Co., Inc., Cranford, NJ 07016. | Doxylamine succinate, Phenyltoloxamine dihydrogen citrate. |
| Whitehall Laboratories, Inc., New York, NY 10017. | Diphenhydramine hydrochloride. |

The following submission was not received in adequate time for review by the Panel:

| *Firm* | *Marketed Product* |
|---|---|
| Del Laboratories, Inc., Farmingdale, NY 11735. | Placin Calmative Capsules. |

2. *Labeled active ingredients contained in these marketed products.*

Acetaminophen, Ammonium bromide, Aspirin, Citric acid, Diphenhydramine hydrochloride, Doxylamine succinate, Methapyrilene fumarate, Methapyrilene hydrochloride, Niacinamide, Passion flower extract, Phenyltoloxamine dihydrogen citrate, Potassium bromide, Pyrilamine maleate, Salicylamide, Scopolamine aminoxide hydrobromide, Scopolamine hydrobromide, Sodium bicarbonate, Sodium bromide, Thiamine hydrochloride.

B. *Request for Submission of Stimulant Drug Data.* Pursuant to the notice published in the Federal Register of May 25, 1973 (38 FR 13763) requesting the submission of data and information on stimulant drugs, the following firms made submissions relating to the indicated products:

1. *Submissions by firms.*

| *Firm* | *Marketed products* |
|---|---|
| Blair Laboratories, Inc., Norwalk, CT 06856. | Pre-Mens Forte Tablets. |
| Bristol-Myers Co., New York, NY 10022. | No-Doz Tablets. |
| Jerrard Cosmetics, Ltd., Hollywood, CA 90028. | Love Garden Stimulant Capsules. |
| J. B. Williams Co., Inc., Cranford, NJ 10017. | Viviran Tablets. |

There were no additional related submissions.

2. *Labeled active ingredients contained in marketed products.*

Ammonium chloride, Caffeine, Ginseng, Vitamin E.

### C. Classification of Submitted Data

1. *Ingredients considered by the Panel for safety and effectiveness as nighttime sleep-aids or daytime sedatives.*

Ammonium bromide, Diphenhydramine hydrochloride, Doxylamine succinate, Methapyrilene fumarate, Methapyrilene hydrochloride, Phenyltoloxamine dihydrogen citrate, Potassium bromide, Pyrilamine maleate, Scopolamine aminoxide hydrobromide, Scopolamine hydrobromide, Sodium bromide.

2. *Ingredient considered by the Panel for safety and effectiveness as a stimulant.*

Caffeine.

3. *Ingredients referred to other OTC panels for review.*

| *Ingredient* | *Panel Referred To* |
|---|---|
| Acetaminophen | Internal Analgestic Panel. |
| Ammonium chloride | Miscellaneous Internal Drug Products Panel. |
| Aspirin | Internal Analgesic Panel. |
| Salicylamide | Internal Analgesic Panel. |

4. *Irrational ingredients.*

The following ingredients in submitted products for review were classified by the Panel as irrational for use and are discussed later in this document:

| *Claimed Ingredient* | *Irrational Use* |
|---|---|
| Ammonium chloride | Stimulant |
| Ascorbic acid | Nighttime Sleep-Aid/Daytime Sedative |
| Citric acid | Nighttime Sleep-Aid/Daytime Sedative |
| Ginseng | Stimulant |
| Niacinamide | Nighttime Sleep-Aid/Daytime Sedative. |
| Passion flower extract | Nighttime Sleep-Aid. |
| Sodium bicarbonate | Nighttime Sleep-Aid/Daytime Sedative. |
| Thiamine hydrochloride. | Nighttime Sleep-Aid. |
| Vitamin E | Stimulant. |

5. *Inactive ingredients.*

Flavoring agents, Coloring agents, Talc.

The Panel is concerned about the carcinogenic potential of asbestos in talc, which is discussed later in this document.

The Panel has included the following table for the convenience of the reader, in which the active ingredients have been categorized:

CATEGORIZATION OF SINGLE AND COMBINATION INGREDIENTS CONSIDERED BY THE PANEL FOR SAFETY AND EFFECTIVENESS AS NIGHTTIME SLEEP-AIDS, DAYTIME SEDATIVES OR STIMULANTS

*(1) Nighttime sleep-aids as single ingredients*

| Ingredient | Category | Justification for categorization [1] | Additional period for testing |
|---|---|---|---|
| Antihistamines: | | | |
| Diphenhydramine hydrochloride | III | S, E | 3 years. |
| Doxylamine succinate [2] | III (MH) | S, E | Do. |
| Methapyrilene fumarate | III | S, E | Do. |
| Methapyrilene hydrochloride | III | S, E | Do. |
| Phenyltoloxamine dihydrogen citrate [2] | III (MH) | S, E | Do. |
| Pyrilamine maleate | III | S, E | Do. |
| Bromides: | | | |
| Ammonium bromide | II | S, E | None. |
| Potassium bromide | II | S, E | Do. |
| Sodium bromide | II | S, E | Do. |
| Scopolamine compounds: | | | |
| Scopolamine aminoxide hydrobromide | II | S, E | Do. |
| Scopolamine hydrobromide | II | S, E | Do. |
| Miscellaneous compounds: | | | |
| Acetaminophen [3] | II | E | Do. |
| Aspirin [3] | II | E | Do. |
| Passion flower extract | II | IR | Do. |
| Salicylamide [3] | II | E | Do. |
| Thiamine hydrochloride | II | IR | Do. |

[1] S (safety), E (effectiveness), IR (irrational combination) and NA (not applicable).
[2] MH indicates ingredient is placed in Category III (marketing hold), with additional data required prior to marketing for use indicated.
[3] Referred to OTC Internal Analgesics Panel for evaluation of analgesic claims.

*(2) Nighttime sleep-aids as combinations of ingredients*

| Combination | Category | Justification for categorization | Additional period for testing |
|---|---|---|---|
| Combinations containing 2 or more antihistamines | II | S, E | None. |
| Combinations containing bromides | II | S, E | Do. |
| Combinations containing scopolamine | II | S, E | Do. |
| Combinations containing analgesics.[1] | III | E | 3 years. |
| Combinations containing thiamine hydrochloride or passion flower. | II | IR | None. |

[1] Referred to OTC Internal Analgesics Panel for evaluation of analgesic claims.

**The Panel was unable to determine other rational combinations which might be considered safe and effective as nighttime sleep-aids.**

*(3) Daytime sedatives as single ingredients*

| Ingredient | Category | Justification for categorization | Additional period for testing |
|---|---|---|---|
| Antihistamines: | | | |
| Diphenhydramine hydrocholride [1] | II | S, E | None. |
| Doxylamine succinate [1] | II | S, E | Do. |
| Methapyrilene fumarate | III | S, E | 3 years. |
| Methapyrilene hydrochloride | III | S, E | Do. |
| Phenyltoloxamine dihydrogen citrate | III | S, E | Do. |
| Pyrilamine maleate | III | S, E | Do. |
| Bromides: | | | |
| Ammonium bromide | II | S | None. |
| Potassium bromide | II | S | Do. |
| Sodium bromide | II | S | Do. |
| Scopolamine compounds: | | | |
| Scopolamine aminoxide hydrobromide | II | S, E | Do. |
| Scopolamine hydrobromide | II | S, E | Do. |
| Miscellaneous compounds: | | | |
| Acetaminophen [2] | II | E | Do. |
| Aspirin [2] | II | E | Do. |
| Salicylamide [2] | II | E | Do. |
| Niacinamide | II | IR | Do. |
| Thiamine hydrochloride | II | IR | Do. |

[1] Ingredients have not been submitted as daytime sedatives and would not be appropriate for such use. (See discussion of individual ingredients in this preamble.)
[2] Referred to OTC Internal Analgesics Panel for evaluation of analgesic claims.

*(4) Daytime sedatives as combinations of ingredients*

| Combination | Category | Justification for categorization | Additional period for testing |
|---|---|---|---|
| Combinations containing 2 or more anthistamines | II | S, E | None. |
| Combinations containing bromides | II | S, E | Do. |
| Combinafions containing scopolamine | II | S, E | Do. |
| Combinations containing analgesics | III | S, E | 3 years. |
| Combinations containing vitamins | II | IR | None. |

**The Panel was unable to determine other rational combinations which might be considered safe and effective as daytime sedatives.**

*(5) Stimulants as single ingredients*

| Ingredient | Category | Justification for categorization | Additional period for testing |
|---|---|---|---|
| Caffeine | I | S, E | NA. |
| Ammonium chloride [1] | II | IR | None. |
| Ginseng | II | IR | Do. |
| Vitamin E | II | IR | Do. |

[1] Referred to OTC Miscellaneous Internal Panel for evaluation of diuretic claims.

*(6) Stimulants as combinations of ingredients*

| Combination | Category | Justification for categorization | Additional period for testing |
|---|---|---|---|
| Combinations containing diuretics | II | IR | None. |
| Combinations containing ginseng | II | IR | Do. |
| Combinations containing Vitamin E | II | IR | Do. |

The Panel was unable to determine other rational combinations which might be considered safe and effective as stimulants.

## II. Nighttime Sleep-Aids

### A. General Discussion

Sleep is generally defined as a regularly recurrent, easily reversible behavioral state characterized by relative quiescence, and a greatly increased threshold of response to stimulation from the environment. In recent years it has been shown that a series of well-defined changes in brain wave patterns and other physiological changes regularly accompany behavioral sleep. These polygraphically recorded patterns are now useful in determining exact time of sleep onset and minute-by-minute changes in sleep stages. It appears justifiable at this point to add to the above behavioral definition of sleep that normal sleep must be accompanied by the usual well-determined sequence of polygraphic patterns.

The Panel accepts that experiencing occasional sleep problems is a valid indication for OTC medication. Sleep problems amenable to help by OTC products would fall into two broad categories: (1) Occasional difficulty in falling asleep (an increase in sleep latency), and (2) occasional difficulty in remaining asleep (an increase in number of awakenings, total time awake after sleep onset, or early morning awakening). Normal sleep patterns vary considerably and a person should take OTC medication only when his pattern deviates widely from his usual pattern.

Patients with severe or chronic insomnia are not candidates for self-medication; they should consult their physicians. Severe insomnia can be defined as sleep difficulty serious enough to interfere regularly with a person's normal waking activities. Chronic insomnia is sleep difficulty occurring every night or almost every night for at least several weeks.

An OTC nighttime sleep-aid, then, is a substance which helps an individual fall asleep or is used for the relief of occasional sleeplessness. Possible uses for such products, if demonstrated by adequate testing, would be to reduce time taken to fall asleep, number of awakenings, or early morning awakening or any combination of the above circumstances if these circumstances (delayed sleep, frequent awakenings, light sleep, or reduced duration of sleep) interfere with the normal sleep pattern of the individual.

### B. Safety and Effectiveness

The Panel suggests the criteria in the discussion below to establish the safety and effectiveness of these agents.

The active ingredient must be safe in the doses suggested on the labeling. The demonstration of safety should be based upon current criteria used to evaluate centrally acting drugs. This includes the Panel's suggested guidelines for testing the safety of a nighttime sleep-aid. (See paragraph II D below—Data Required for OTC Nighttime Sleep-Aid Ingredient Evaluation.) The general guidelines used in the introduction of drugs for prescription use should also be followed in assessing safety. Also, certain special types of adverse reactions are difficult to evaluate. For example, teratogenic effects (the ability to cause congenital malformations), are so difficult to determine before marketing that the Panel advises that new drugs not intended for life-saving use should not be used in women known to be pregnant or who are nursing a baby, and this precaution should be included in the labeling. Further, drugs that are suspected of causing mutations and/or cancer should not be authorized for OTC use. Finally, untoward interactions between an OTC preparation and other commonly used drugs or foods should be indicated in the labeling if such interactions may cause severe discomfort, distress, disease, or disability.

Because these drugs are intended for nighttime use, their action should not persist into the daytime hours, or beyond the intended period of sleep, so that no interference with normal motor or sensory performance is encountered during the waking state.

The drug should be effective without causing undue disturbance in the period after sleep, such as depressed motor or sensory activity, including reduced ability to perform simple motor tasks. The drug should not interfere in an unusual manner or to an unusual degree with physiological EEG patterns characteristic of normal sleep.

There should be a low potential for allergic manifestations and for idiosyncratic responses to the drug. The margin between an effective and a toxic dose should be large, and the desired effect should be produced ordinarily with a single dose; occasionally a repeated dose may be needed. The drug should not be habit-forming or addicting. There should be no serious toxicity that would result from ill-advised or inadvertent chronic use of the drug.

Determination of effectiveness of an OTC nighttime sleep-aid can be made to some extent by subjective reports from patients or subjects, and by nurses' observations, but are made more accurately by all night sleep laboratory recordings. Preferably, several methods should be used, such as all night sleep recordings in a small number of subjects combined with subjective reports in a large number of subjects, to make certain that a potential sleep-aid does improve sleep as verified both by objective criteria and by reports of improved sleep by the subjects themselves. The Panel has included recommended guidelines for evaluating the effectiveness of a nighttime sleep-aid. (See paragraph II D below—Data Required for OTC Nighttime Sleep-Aid Ingredient Evaluation.)

In accordance with current practice, the packaging of such drugs should be designed to protect small children. In addition, the Panel believes that the quantity of the drug available in an OTC nighttime sleep-aid product container should be limited to prevent accidental ingestion of a lethal dose.

*Labeling*

Consumers often have a variety of questions regarding OTC medication. Additionally, they may need to discuss, or be warned of, possible drug interactions such as with certain other central nervous system depressants (e.g., tranquilizers, antihistamines, hypnotics, alcohol). For this reason, the Panel is of the opinion that all OTC products, and particularly those in the daytime sedatives, and nighttime sleep-aids categories should contain the following general warning: "Do not take this product if you are presently taking a prescription or OTC drug without consulting a physician or pharmacist."

The Panel is aware that the Commissioner, in the Federal Register of June 4, 1974 (39 FR 19880), has exhaustively reviewed the question of drug interactions and has ruled that specific warnings should replace general statements.

However, the Panel concludes that OTC nighttime sleep-aids are a class apart. Their specific and potentially hazardous actions as central nervous system depressants render them especially liable to additive toxicity with other depressant drugs used concurrently, whether prescription or OTC. The danger is compounded by the layman's ignorance of even the possibility that he might be exposing himself to the cumulative toxic effects of two or more depressant drugs. For example, he may already be taking remedies for a variety of indications (e.g., cough/cold, antimo-

tion, dermatologic, etc.), and be unaware that these products contain antihistamines or other centrally acting ingredients. In this special case, therefore, the Panel believes it important that the general warning be retained for the guidance of the consumer.

The recommendation that the consumer who purchases an OTC drug should consult with a pharmacist is based on the belief that the pharmacist is the most readily available community health professional to the purchasing consumer, and that the average U.S.A. pharmacist today is probably as well acquainted with OTC preparations and the subject of possible drug interactions, etc., as the average physician. As a specialist in the drug field, he possesses knowledge of the subject, or will probably have appropriate written material (e.g., product information, handbooks, manuals, drug interaction lists) readily available.

Based upon the foregoing general discussion of the pharmacology of nighttime sleep-aids and limitations inherent therein, the following are valid (Category I) claims for nighttime sleep-aids:

"Helps fall asleep" and "For relief of occasional sleeplessness."

The following warnings should be included: "For adults only. Do not give to children under 12 years of age." "Take this product with caution if alcohol is being consumed."

The following warning on products containing antihistamines should also be included: "*Caution:* This product contains an antihistamine drug."

The labeling should also state that OTC nighttime sleep-aids are only recommended for the treatment of occasional sleep difficulty. The following warning should appear on the label: "If condition persists continuously for more than 2 weeks consult your physician. Insomnia may be a symptom of serious underlying illness."

The following Category III labeling claims are possibly valid if supported by controlled studies:

"Reduces time to fall asleep in persons with difficulty in falling asleep." "Reduces number of awakenings in persons who wake frequently during the night." "Prolongs sleep."

The following terms currently used are classified as Category II because they are seriously misleading or ambiguous: "natral sleep, normal sleep, sound sleep, non-habit-forming, guaranteed (fast acting), or refreshing sleep."

"Natural sleep" is ambiguous since "natural" is not a well-defined term and could have referred to a natural feeling state in the morning or to normal appearing sleep by any number of physiological criteria. The term is misleading when these drugs are taken, since the drug is an exogenous non-naturally occurring agent introduced into the body. Hence, the body is obviously not entirely in its "natural" state during drug-induced sleep.

"Normal sleep" is ambiguous and is misleading for the same reasons given under natural sleep. "Sound sleep" is similarily ambiguous. The term "non-habit-forming" is misleading, undesirable and probably false because it is very hard to prove that any product with psychotropic activity can be non-habit-forming; but more importantly, there is an insinuation that other OTC sleep-aid products obviously are habit-forming.

"Guaranteed" is misleading and a false promise if used in a general way such as "guaranteed fast-acting." No drug helps 100 percent of the time. The Panel believes that the word "guarantee" should be prohibited in regard to medical claims. The Panel will not comment on the use of the term in labeling when it refers to promotional consideration such as "Guarantee: Your money will be refunded without question if you are in any way dissatisfied with this product."

"Refreshing sleep" is misleading and ambiguous since in the opinion of the Panel, "refreshing" is extremely difficult to define.

The Panel concludes that approval of an active ingredient or combination of active ingredients for a particular indication should not be interpreted as unique to the active ingredient or to the combination. Labeling, package insert, or advertising shall not refer to such approval either directly or by inference as a unique or an exclusive endorsement of such an ingredient or combination of ingredients.

The Panel is aware that the Food and Drug Administration does not regulate the advertising of OTC drug products. However, the Panel recommends that advertising in any medium for these drugs that in any way uses the labeling, package, or container not be inconsistent, even in subtle implication through mood, focus or innuendo, with the labeling claims in the proposed monographs. It follows that labeling and advertisements should, therefore, be closely monitored by the proper authority to see that advertisements do not go beyond the limitations of the monograph and/or negate the restrictions and warnings recommended by the Panel.

### C. CATEGORIZATION OF DATA

1. *Conditions under which nighttime sleep-aids are generally recognized as safe and effective and are not misbranded.*

*Active Ingredients*

The Panel concludes that none of the submitted active ingredients is generally recognized as safe and effective and are not misbranded as nighttime sleep-aids.

*Labeling*

The Panel recommends the following general labeling for nighttime sleep-aid active ingredients to be generally recognized as safe and effective and not misbranded:

a. *Indications.* (1) "Helps fall asleep." (2) "For relief of occasional sleeplessness."

b. *Warnings.* (1) "For adults only. Do not give to children under 12 years of age." All studies reviewed by the Panel deal with adults; and not enough data are available on these drugs for children. Also, there are insufficient data on how children will react, especially in light of the fact that many children have an opposite reaction to that of adults. For example, it is possible that children may be more easily stimulated rather than sedated with antihistamines used as nighttime sleep-aids (Ref. 1).

(2) "Do not take this product if pregnant or if nursing a baby." The reason for this warning is that the Panel feels there have not been enough studies regarding teratogenicity of these drugs. The use of any drug in pregnancy or during lactation should therefore be carefully assessed. Also, with respect to nursing mothers, it should be noted that many nighttime sleep-aid drugs, for example, antihistamines, possess anticholinergic properties which may inhibit lactation.

(3) "Do not take this product if you are presently taking a prescription or other OTC drug, without consulting your physician or pharmacist." The Panel believes that self-medication under such circumstances may lead to a drug interaction or overdose situation. For example, if an individual cannot sleep because of a cold or allergy he may unwittingly use an OTC antihistamine nighttime sleep-aid and at the same time use an antihistamine cold or anti-allergy preparation. This may result in excessive sedation or confusion.

(4) "If condition persists continuously for more than 2 weeks, consult your physician. Insomnia may be a symptom of serious underlying medical illness." The Panel is concerned that individuals may tend to overuse psychotropic drugs instead of seeking proper medical treatment of underlying emotional disturbances. The Panel considers that OTC nighttime sleep-aids are only for short-term occasional sleeplessness experienced by some "normal" individuals and that use of an OTC nighttime sleep-aid continuously for more than 2 weeks may be indicative of a more serious condition.

(5) "Take this product with caution if alcohol is being consumed." The Panel is aware that there may be additive effects if alcohol is taken in addition to other central nervous system depressants, such as OTC nighttime sleep-aids and prescription hypnotics, sedatives and tranquilizers. These additive effects include excessive sedation, confusion and, in extreme circumstances, may result in coma and even death.

(6) For products containing an antihistamine: "Caution: This product contains an antihistamine drug."

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2. *Conditions under which nighttime sleep-aids are not generally recognized as safe and effective or are misbranded.* The use of nighttime sleep-aids under the following conditions is unsupported by scientific data, and in many instances by sound theoretical reasoning. After carefully reviewing all data submitted, the

Panel concludes that the following ingredients, labeling, and combination drugs involved should be removed from the market:

ACTIVE INGREDIENTS

Bromides: Ammonium bromide, Potassium bromide, and Sodium bromide.
Scopolamine Compounds: Scopolamine aminoxide hydrobromide, and Scopolamine hydrobromide.
Miscellaneous Compounds: Acetaminophen, Aspirin, Passion flower extract, Salicylamide, and Thiamine hydrochloride.

a. *Bromides (ammonium, potassium, sodium)*. The Panel concludes that ammonium bromide, potassium bromide and sodium bromide are not safe in therapeutic dosage levels as OTC nighttime sleep-aids because of toxicity and possible teratogenic effects. The Panel further concludes that at the dosage levels presently marketed these ingredients are not effective as nighttime sleep-aids. Ammonium, potassium and sodium bromides are similar in their pharmacological action and will be discussed as a group.

Bromine was discovered by Balard in 1826 and introduced into medicine in the salt form for the treatment of epilepsy in 1843 by Laycock. Its application as a hypnotic by Behrend dates back to 1864 (Ref. 1). The toxicity of bromides was noted in the 19th century. Wuth in 1927 reemphasized the toxicity of bromides which had been ignored for almost 100 years (Ref. 2). The barbiturates replaced bromides in the treatment of epilepsy, and bromides came to be used mainly as hypnotics and sedatives in the early 20th century.

By the late 1920's, bromides were widely prescribed and sold OTC as sedatives and hypnotics. Modern case reports about bromide toxicity recall their widespread use and importance before barbiturates and the so-called "minor tranquilizers" such as meprobamate replaced them to a very large extent in the 1950's (Ref. 3). With the availability of more prescription drugs, the use of bromides shifted primarily to OTC use, although cases of poisoning still result from prescribed drugs. The OTC preparations have become the largest source of bromide use today in medicine. They are seldom recommended by physicians although toxic effects have resulted from prescriptions containing bromides (Ref. 4) within the past 10 years.

Bromide, the negatively charged ionic form of bromine, is the drug we are concerned with in this review. Its close chemical relation to the chloride ion should be noted. Both chlorine and bromine are chemical elements included in a group known as the halogens. Special analytical methods are needed to detect bromide ion in the presence of chloride ion in biological fluids (Refs. 5 through 11). Bromides are ordinarily given by mouth and are efficiently absorbed. At high doses, subjects complain about gastrointestinal irritation, even when the drugs are given after meals, and some physicians in the past recommended that the bromides be given daily in three divided doses (Ref. 12). Divided doses cut down the intensity of gastrointestinal irritation, but serve no other purpose. A daily dose, if it could be tolerated without gastrointestinal irritation, would maintain therapeutic levels of bromide in the body. Absorption of a single oral dose is complete in 2 to 3 hours according to a study with radioactive bromide ($^{82}$Br) (Ref. 13). Peak plasma levels are reached about 30 to 45 minutes after a single oral dose (Ref. 14).

Distribution of bromide is the same as distribution of chloride, except for certain relatively minor differences. Like chloride, bromide distributes through the extracellular space, which is approximately 21 percent of total body weight. For a 150 lb. (70 kg.) man, the chloride or bromide etracellular space is 14.9 liters or approximately 15 liters. This space includes interstitial fluid and blood plasma. Large amounts of bromide appear in the salivary glands and also in gastric juice, where hydrogen bromide is formed. Bromide secretion by the gastric mucosa is analogous to that of chloride (Ref. 15). Formation of hydrogen bromide contributes to the gastric discomfort experienced by chronic users of bromides. Like chloride, bromide enters the red blood cells in appreciable amounts. Monovalent inorganic anions like chloride or bromide are not bound to any considerable extent to plasma protein, so that plasma determinations of these two ions refer to free halogen.

The total halogen concentration in the extracellular space, as measured in the plasma, is predominately chloride, and is normally about 99 to 105 milliequivalents per liter (mEq/l). In cases of poisoning by bromide, the chloride concentration may appear to go up, and this may be a clue to bromide poisoning. Usually bromide simply replaces part of the chloride, and standard laboratory tests report both ions as chloride.

Bromide does not penetrate cells in the brain to a greater extent than chloride, nor has there been found any qualitatively different distribution in brain tissue. It is assumed that bromide acts directly on the central nervous system (CNS), but not much information is available about the mechanism of its action. This is due, in large part, to the fact that bromides have been less widely used in the modern era in which more sophisticated ways of monitoring central nervous system function were introduced.

At least 80 percent of the elimination of bromide proceeds via the kidney. Both chloride and bromide ions are cleared from the kidney by simple filtration, and then each is partially reabsorbed by the tubules of the kidney. The renal clearance of bromide is slightly less than that for chloride because the bromide ion is reabsorbed from the renal tubules somewhat more efficiently than chloride (Ref. 16). If chloride intake is kept constant and enough bromide is given, it is possible to reach high steady state levels of bromide. If bromide intake is maintained constant and chloride intake is reduced, there will be a more rapid increase in the body concentration of bromide. The half-time for elimination of bromide from the body is about 12 days, on the average, for persons with normal kidney function (Ref. 13), assuming that sodium chloride intake remains constant.

The maintenance dose of bromide, about 0.9 gm per day, if taken from the start of dosing, would produce no ill effects, because almost 6 weeks would elapse before effective concentrations would be attained in the body fluids. This rate of accumulation is much too slow, since no one taking the drug on his own volition would wait that long for symptomatic relief; thus, large doses have to be taken initially to produce an effect rapidly. If dosage continues at the same high initial rate, cumulative poisoning would soon occur. At a moderate dose of 1 gm 3 times a day, the minimal effective blood concentration of 50 mg/100 ml is only attained after a week. After 3 weeks of continuous administration at the same rate, the blood level rises to 110 mg/100 ml, a blood concentration likely to produce toxic effects such as rashes, mental disturbances consisting of impaired thought and memory, dizziness and irritability (Ref. 17).

The body content of bromide may increase to a toxic level if the dosage is greater than the required maintenance dose and/or the renal elimination is below the expected level. At a steady rate, where intake equals output, the blood level will be just below the toxic range. If the rate of elimination were reduced, not unusual in older persons, the new steady state blood level of bromide would be a toxic concentration.

The blood serum concentration associated with toxicity is usually reported as 150 mg bromide per 100 ml or above. But cases of toxicity have occurred with serum levels of 50 mg/100 ml, and some patients have tolerated blood levels higher than 150 mg (Ref. 18).

To use these drugs chronically without monitoring the patient's chloride balance and blood serum bromide is, in the Panel's view, not safe medical practice since small changes in chloride intake or small changes in kidney function can lead to severe poisoning.

In 1927, Wuth stated, "Taking into account the interaction of bromides and chlorides, it is evident that if these individual variations of chloride intake are not considered it is merely a matter of luck whether bromide treatment is successful or not, or whether it does or does not lead to intoxication" (Ref. 2).

Depression of the central nervous system occurs with therapeutic amounts of bromides. With low doses and individual becomes drowsy. Larges doses produce impairment of central function, causing difficult speech, difficulty in thinking, and impaired memory.

There has been considerable argument about the effects of bromides on motor performance, but very little research has been done. In a "semiblind" study by Uhr and collaborators (Ref. 19), several tests of motor coordination, including simulated automobile driving, tests of

memory, and behavioral profiles were studied comparing a placebo, meprobamate and bromide. One group was not told what they were ingesting and the other group receiving different amounts of bromide were told that they were all ingesting the same amount. This is a bizarre design. In the doses used, 5.8 gm of bromide per day, there were no major deficits in performance produced by the bromides.

Jellinek and his associates (Ref. 18) inquired about the effects of bromides on human subjects as one increased the blood levels from sedative to mildly toxic ranges. The study was designed so that bromide levels of about 100 to 200 mg/100 ml of serum would be achieved and monitored in normal and psychotic subjects. Physical and psychological examinations were carried out during the course of the study. By giving daily doses of 50 mg of sodium bromide per kg body weight to all subjects, 78 normal subjects attained a mean serum bromide level of 148 mg/100 ml (range 120 to 200). However, a mean of 134 mg (range 98 to 186) was attained in 20 psychotic subjects.

In the normal subjects only sedative effects were noted. "Sounder and increased sleep" and some loss of concentration were noted. Skin rashes were seen in 2 of the 78 subjects. Some moderate tremors of the tongue, slightly increased patellar reflexes, and subjective feelings of "unsteadiness" were noted. Psychological tests that 44 percent (6 subjects) had reduced ability to concentrate. Sixteen subjects volunteered the information that they had developed a sexual indifference. Of the 20 psychotic patients with blood levels comparable to those for normal subjects, 2 showed sluggish or fixed pupillary reactions to light. Except for these there was "generally a picture of sedation and even of some therapeutic effect."

In the same study (Ref. 18), in a second group of 28 psychotic patients, doses of 75 to 100 mg/kg body weight of sodium bromide were given daily. A mean blood serum level of bromide of 228 mg/100 ml was obtained (range 175 mg to 310 mg). Sixteen subjects were dropped from the study after the fifth week because of various toxic signs. These signs included positive Romberg test (6 subjects), bromoderma (2 or possibly 3), unsteadiness and/or dizziness in 4, sleepiness or similar symptoms in 8, and a few miscellaneous toxicities. "An exacerbation of psychotic symptoms was not prominent" in this whole group of 28 subjects.

The Panel notes that the conclusion reached by the authors is that bromide therapy does not uncover psychotic behavior, but that psychotic patients generally show the same kinds of symptoms reported for normal subjects who are intoxicated. It is suggested by the authors that at blood levels below 200 mg bromide/100 ml of serum an additional factor is at work in cases where "bromism" or "bromide psychosis" have been reported.

Various types of skin rashes are seen in cases of bromide toxicity. The diagnosis is often missed because the possibility of bromide ingestion is not considered by the physician (Refs. 20 and 21). Because these reactions occur in only 1 to 10 percent of subjects taking bromides, it is likely that they represent an allergic reaction to the drug.

A single oral dose of bromide is not effective, because it takes a few days to achieve a therapeutic concentration in the extracellular fluid. This means that the sedative activity will be persistent and not transitory, as is intended when a hypnotic (sleep inducer) is used to induce sleep. Because bromides cannot induce sleep promptly after a single dose and must be used for several days and because these ingredients then have a continued pharmacological action, the Panel believes bromides should not be indicated as OTC sleep-aids. Sleep is not induced, says Sollman (Ref. 1), but is made possible by the calming action: "* * * the bromides tend to produce a mental, calm, aloofness progressing to lassitude. These predispose to sleep which can be resisted."

The Panel notes that contraindications to bromide therapy have been listed repeatedly (Ref. 22). These include: (1) Anorexia: Vomiting and diarrhea induced by taking of bromides can easily deplete the body's chloride content, thus making chronic bromide intoxication more easily produced, (2) Alcoholism: Bromides enhance and prolong symptoms of hangover and intoxication, (3) Congestive heart failure: Usually patients with cardiac failure are on a restricted salt diet, so that intoxication with bromides will occur more readily than in normal subjects, and (4) Kidney disease: Excretion of bromides is likely to be reduced more than in the normal individual and toxicity is to be anticipated.

Depression of the entire central nervous system is the usual pharmacological effect, except that the medulla is not depressed until very high drug concentrations are achieved. Psychic functions are depressed and spinal reflexes are diminished. Muscle tone is lowered. Large doses lessen arterial tension, lower body temperature, depress sexual drive, and cause somnolence, loss of coordination and sluggish reflexes, Psychic phenomena may include hallucinations of auditory or visual type, depression, or maniacal excitation. The neurological examination usually, but not always, shows a symmetrical distribution of altered function. This is useful in distinguishing between a central lesion and intoxication.

There has been discussion in the literature about the distinction between true schizophrenia and the apparent schizophrenia exhibited by some patients with bromide intoxication. Clearing up of the symptoms and their nonrecurrence as the intoxication disappears is a useful index. Some authors, for example, Levin (Ref. 23), claim that they can distinguish the two types of patient by the content of their hallucinations.

Neurological symptoms are commonly observed in cases of poisonings. Weakness was most common in one study of 27 cases (Ref. 24). It can involve a single extremity and thus mimic a central nervous system tumor or cerebrovascular accident. Sleepiness and stupor were also common. The state of consciousness was depressed in 14 of the patients, varying from drowsiness to coma. Thirteen patients were incontinent. Twenty had abnormal reflexes. Ataxia with the appearance of intoxication was the most common cerebellar sign; coarse tremor of the hands or tongue was seen in seven patients. Slurred speech was also common. Psychic manifestations included extreme excitement (12 cases), emotional instability, confusion, disorientation, and incooperativeness. In 12 cases, the average bromide concentration was 239 mg/100 ml of blood serum. Most of these patients had bronchopneumonia and/or urinary tract infection. The two deaths were due to pneumonia, a frequent cause of death in comatose patients.

"Ocular bobbing" is an intermittent conjugate downward deviation of the eyes in the absence of any reflex lateral eye movements. It is ordinarily caused by destruction of part of the brain. The sign is also seen in cases of bromism where there is a lateral deviation of the eyes as well as the downward movement (Ref. 25).

Animal studies have pointed to the possibility that bromides may be teratogenic (cause abnormalities of the developing fetus) (Ref. 26). In studies carried out on animals with chronic bromide intake such that the concentration in the body was about as great as in human subjects on therapeutic doses, there appeared to be mental retardation as evidenced by reduced learning ability in offspring (Ref. 27). In this case, the bromide was given to pregnant rats from the 4th to 12th day of gestation at a total dosage of 192 mg of bromide per kg.

A woman who had previously had two normal children delivered two boys, 1.5 years apart, while taking bromides. Both boys showed growth retardation and reduced head size. One was described as a "true microcephalic" (Ref. 28).

It is clear that bromides cross the placenta readily. Cases of bromide intoxication have occurred in newborns. A girl born after 40 weeks of gestation weighed only 2,020 gm (4.45 lb), was irritable and difficult to feed in the posnatal period and developed slowly. At age 2.5 years, she showed retarded mental and motor development and was below the 10th percentile in height, weight, and skull circumference. The mother had taken large amounts of a bromide-containing preparation all through gestation to relieve headaches (Ref. 29).

A 7-day-old girl entered a children's hospital with lethargy and poor sucking reflex and a blood serum bromide level of 365 mg/100 ml. The mother, a nurse, took 1 quart of an OTC bromide preparation the day before delivery and had appar-

ently taken lesser amounts during her 39-week pregnancy. On the 6th post partum day, the mother was found to have a serum bromide of 320 mg/100 ml. Both mother and infant recovered in this case, even though the blood levels were quite high (Ref. 30). A case of bromism with skin rash present was detected in a premature male infant. Ten days after delivery, skin lesions began to appear and penicillin treatment was started. The penicillin did not affect the rash, and it was suggested that the mother's milk be tested for bromide. The milk contained 120 mg bromide per 100 ml. The child was cured by substituting cow's milk (Ref. 26).

There are numerous case reports of bromide poisoning in infants (Ref. 31).

In summary, the Panel concludes that because the mode of action of the bromides involves displacement of chloride, a normal body constituent, and because this displacement takes many days to occur after ingestion of many of the "recommended" doses, the bromides cannot be considered for the use of occasional symptoms of sleeplessness. The mode of action involves a disturbance in the body's salt balance which requires the therapeutic level of the drug to be very close to the toxic level. In addition, bromides readily cross the placental barrier which might result in teratogenic effects such as mental retardation of the offspring. Since bromides offer only a narrow margin of safety resulting in a small or negligible benefit-to-risk ratio, the Panel does not believe that further testing is warranted.

Further, while it is possible to treat epilepsy with bromides (although more convenient drugs now exist for this purpose), blood levels must be constantly monitored and dosage must be individualized. Since monitoring of this type is not feasible or reasonable for an OTC drug and since this is an indication which cannot be labeled for use by a lay person without the advice and supervision of a physician, the Panel concludes that there is no indication for which bromides should be available on the OTC market. The risks involved in the uncontrolled use of bromides as nighttime sleep-aids are too great to permit general availability in the OTC market (Refs. 32 through 37). Because of the inherent safety issues, no further testing for safety and effectiveness is advised.

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b. *Scopolamine compounds.* The Panel concludes that scopolamine, scopolamine hydromide, and scopolamine aminoxide hydromide are not safe at dosage levels which might possibly be effective as OTC nighttime sleep-aids. Although there are insufficient data available for OTC nighttime sleep-aid products concerning the effectiveness of scopolamine alone in producing sleep, the Panel believes, on the basis of the reported toxicity associated with these compounds, that doses high enough to be possibly effective as OTC nighttime sleep-aids are not safe. In the dosages currently used it is considered ineffective in the Panel's view as an OTC nighttime sleep-aid.

Scopolamine (L-hyoscine) occurs naturally as an alkaloid of belladonna. It is chemically and pharmacologically similar to atropine. Scopolamine in clinical doses (0.5 to 1.0 mg, orally or parenterally) normally causes drowsiness, euphoria, amnesia, fatigue, and dreamless sleep (Ref. 1). Meyers and Abreu (Ref. 2) suggest that differences in the therapeutic potencies of atropine and scopolamine may produce dissimilar effects in the brain.

Selected doses of either drug produce sedation in animals. Large doses of scopolamine (1.0 to 1.5 mg/kg) produce persistent excitement and larger doses produce transient excitement followed by deep sedation (Ref. 2). The sedative effects of scopolamine in man appear with doses of 0.3 to 0.6 mg whereas 2.0 mg or more of atropine are required to produce sedation, amnesia, and drowsiness (Ref. 3).

The belladonna alkaloids are absorbed, rapidly from the gastrointestinal tract, more so from the intestine than the stomach (Ref. 4). They also enter the circulation when applied locally to the mucosal surfaces of the body. Only limited absorption occurs from the eye and the intact skin, but in the lung atro-

[1] Cited OTC Volumes refer to the submissions made by interested persons pursuant to the call for data notices published in the FEDERAL REGISTER of August 22, 1972 (37 FR 16885) and May 25, 1973 (38 FR 13763). 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.

pine can be absorbed sufficiently from inhaled smoke to produce extrapulmonary effects such as blockade of peripheral symptoms due to cholinergic stimulation (Ref. 5).

Only about 1 percent of an oral dose of scopolamine is eliminated in the urine. Much of the alkaloid is thought to be destroyed by enzymatic hydrolysis, particularly in the liver.

Tolerance to scopolamine apparently occurs, although experimental evidence for it is sparse. Studies in mice suggest that tolerance occurs when scopolamine is given chronically to antagonize pilocarpine-induced hypothermia (Ref. 6). Tolerance did develop to scopolamine's effects in a behavioral situation in which chronic doses were injected into rats (Ref. 7). However, other workers have found no tolerance to scopolamine in mice when the drug was given chronically and then withdrawn to test the effects of pilocarpine (Ref. 8).

Studies in humans strongly suggest that chronic scopolamine administration (10 mg/kg intramuscularly) produces tolerance to the central nervous system as well as some involuntary (autonomic) effects (Ref. 9). Tolerance is noticed particularly in patients with parkinsonism, who may eventually receive daily doses of scopolamine that would result in toxic levels, if given to patients receiving the drug for the first time (Ref. 10).

Habituation and true addiction probably do not occur, although the literature on this aspect of scopolamine's actions is also sparse. In patients with parkinsonism who are suddenly withdrawn from large therapeutic doses, vomiting, malaise, sweating, and salivation have been known to occur (Ref. 1).

The side effects with therapeutic doses are mainly of importance because of their subjective unpleasantness to the patient and include the following: (1) dryness of the mouth, (2) blurred vision, (3) photophobia (abnormal visual intolerance of light), and (4) cardiac effects (tachycardia, bradycardia, arrhythmias, and palpitations). These are the most common side effects, and can rarely be completely avoided with the doses required to obtain significant therapeutic benefit (Ref. 11). Tolerance to the side effects, as with the therapeutic doses, apparently occurs.

Other side effects which sometimes occur include the following: (1) acute glaucoma, (increased intraocular pressure), (2) constipation, which can progress into complete obstruction of the bowel, (3) urinary retention, when enlargement of the prostate is present, (4) anhidrosis (lack of sweating), which may produce heat intolerance and in some cases can seriously impair body temperature regulation in individuals in a hot environment (children are especially sensitive to this effect), (5) hypersensitivity reactions, particularly skin rashes, and occasional edema (swelling) of parts of the mouth and throat, (6) ataxia, manifested by stumbling or difficulty in walking, may be seen with therapeutic doses in susceptible individuals; and (7) toxic psychoses (hallucinations, agitated delirium, belligerence, violence) may occur, particularly when scopolamine is combined with bromides or methapyrilene, and taken in high doses (Refs. 12 and 13). In a report involving scopolamine given as a premedication before surgery, 20 percent of the patients given 0.2 to 0.6 mg intravenously became delirious postoperatively (Ref. 14).

It has been reported that the sedation, tranquilization, and amnesia produced by scopolamine are useful in many circumstances, including labor, delirium tremens, toxic psychoses, and maniacal states (Ref. 1). In these conditions, the drug is almost always combined with agents which produce analgesia and sedation. However, given alone in the presence of pain or severe anxiety, scopolamine may induce outbursts of uncontrolled behavior.

As indicated earlier, therapeutic doses of scopolamine normally cause drowsiness, euphoria, amnesia, fatigue, and dreamless sleep. The same doses, however, occasionally cause excitement, restlessness, hallucinations, or delirium instead (Ref. 1). These atypical reactions may be idiosyncratic (unusual, infrequent, genetically caused reactions). They resemble the central effects of toxic doses of atropine, and occur regularly after large doses of scopolamine.

Infants, young children, and old people are especially susceptible to the effects of an overdose of scopolamine. The symptoms of poisoning develop soon after ingestion of the drug. The mouth becomes dry and burns; swallowing and talking are difficult, and there is marked thirst. The vision is blurred, and photophobia (sensitivity to light) occurs. The skin is hot, dry, and flushed. A rash may appear especially over the face, neck, and upper part of the trunk. The body temperature rises and may reach 109° F or higher in infants. The pulse is weak and very rapid, but in infants and old people the increased heart rate may not occur. Palpitations are prominent, and the blood pressure is elevated. Urinary urgency and difficulty in urination are sometimes noted.

The patient is restless, excited, confused, and exhibits weakness, giddiness, and muscular incoordination. Walking and talking are disturbed. Nausea and vomiting sometimes occur. The behavioral and mental symptoms may suggest an acute organic psychosis. Memory is disturbed, orientation is faulty, hallucinations are common, and mania and delirium often occur. In some cases of scopolamine poisoning, a mistaken diagnosis of acute schizophrenia or alcoholic delirium has been made, with the individuals being committed to a psychiatric institution for observation and treatment (Ref. 13). The entire syndrome often lasts 48 hours or longer. Depression and circulatory collapse occur only in cases of severe intoxication; the blood pressure declines, respirations become inadequate, and finally respiratory failure occurs after a period of paralysis and coma.

Fatalities from scopolamine are rare, but sometimes occur in belladonna poisoning in children. In these cases, the cause of death is apparently uncontrolled fever. Of all the potent alkaloids, atropine is usually stated to be more toxic than scopolamine, but the evidence for this is inconclusive; persons have survived doses of 500 mg of scopalmine. (In the case of atropine, doses of 1,000 mg have been survived.) The best antidote for scopolamine is physostigmine (Ref. 15), 2 to 3 mg subcutaneously every 2 hours as needed.

As with any depressant drug, the actions of scopolamine can be expected to enhance the effects of or be enhanced by other depressants such as alcohol (Ref. 16), barbiturates, narcotics, or tranquilizers. The drug has also been shown to produce an acute psychotic reaction when combined with marijuana (Ref. 17).

The following study plus many other studies suggest a "depressant" effect of scopolamine in animals which could be extrapolated to a depressant, or sedative, effect in humans. The dosages used cannot accurately be compared to those used in humans, but they do demonstrate that all of scopolamine's effects in animals are in the range of 0.01 to 10.0 mg/kg when given by injection.

Longo (Ref. 18) studied the effects of atropine and scopolamine on the encephalogram of the rabbit. The two alkaloids produced a sleep pattern (slow synchronous activity) while blocking the "awakening reaction." Scopolamine was 10 to 15 times more active than atropine in this regard. The generally classified EEG synchronization is "dissociated" from the behavioral effects of the drug in that the animal is apparently alert during the time that the EEG indicates a sleep pattern. This is known to be a characteristic of antimuscarinic central action.

The bulk of the literature on scopolamine's effects in man concerns its actions as an antimotion sickness and antiparkinsonism drug. This literature really tells us nothing more than the fact that scopolamine somehow depresses those areas of the brain involved in motion sickness (e.g., the cerebellum, semicircular canals and associated structures, and/or the medually emetic centers) and parkinsonism (basal ganglia and extra pyramidal system), and that the doses used are similar to those which appear to be effective in producing drowsiness.

The number of papers which document the sleep-inducing effects of scopolamine is surprisingly small, and many of these are reviews which assume the sedative effect of scopolamine, or simply refer again and again to the few papers available.

Very early reports in the European literature document the use of scopolamine hydrobromide in producing amnesia during labor when given in doses of $\frac{1}{100}$ gr (0.6 mg) intravenously. This preceded its use in combination with morphine to produce "twilight sleep" as a form of obstetrical analgesia with amnesia. Orkin et al. (Ref. 19) have studied

atropine and scopolamine as preanesthetic medications and have found that smaller quantities of thiopental and meperidine are required to produce unconsciousness when scopolamine (0.4 to 0.6 mg intravenously) is given as a preanesthetic medication. One of their conclusions was that "scopolamine in 0.4 to 0.6 mg doses (intravenously) is almost as hypnotic as 100 mg of meperidine."

Tesoriere (Ref. 20) has also confirmed the "depression of the cortex" and amnesic effects in patients being prepared for surgery. The "common dose" of 0.32 to 0.43 mg (intravenously) can severely depress the older patient and must be used with caution.

Ostfeld and Aruguete (Ref. 21), in an often-cited study, reported that 0.8 mg of scopolamine injected subcutaneously can impair performance on behavioral tests involving the ability to focus attention, to recall objects and words, and to maintain an attentive set. They also noted that whereas the administration of atropine was accompanied by a rise in pulse rate, scopolamine administration was followed by a decrease in such rate. Finally, the subcutaneously administered scopolamine appeared to induce sleep, hallucinations, and mental disorientation more frequently than 10 mg of atropine administered orally.

Eger (Ref. 4), in a very complete review, reaffirmed the central nervous system effects of scopolamine, and noted that scopolamine is some 5 to 15 times more potent in producing drowsiness than atropine.

Environmental conditions and subjective attitudes greatly influence the response to scopolamine. Although these factors have not been extensively studied, a few examples are available (Ref. 22): The pain of labor can cause the response to amnesic doses of scopolamine to change to a state of delirious excitement and restlessness, often to such a degree that restraints are necessary; (2) the loss of a night's sleep can markedly increase the psychotomimetic effects of scopolamine; and (3) in high ambient temperatures, the central effects of scopolamine are significantly accentuated. The mechanism for this last effect is unclear.

The Panel concludes from the available literature that scopolamine definitely has central depressant effects in animals, and that it produces drowsiness and sleep in humans, in appropriate dosages. However, there is a serious lack of sufficient data on the central effects of scopolamine over a wide range of doses in man.

(1) *Scopolamine hydrobromide.* There are products presently on the OTC market promoted for sleep which contain 0.25 mg of scopolamine hydrobromide per unit dose, as part of a combination of ingredients. The Panel concludes that this ingredient is not effective as a nighttime sleep-aid in doses presently marketed, and that at higher, possibly more effective doses it would not be safe.

Although scopolamine hydrobromide has central depressant effects in animals, the evidence for its hypnotic effect in humans is mainly anecdotal on the basis of the drug's early use in parkinsonism and motion sickness. One source, also anecdotal, states that an oral dose of 0.3 mg has "little soporific effect" (Ref. 23). However, the Panel has been unable to locate any clinical studies of the effects of scopolamine hydrobromide alone on sleep onset or duration of sleep.

As mentioned earlier, the Panel has found evidence (Ref. 11) which suggests an alarming frequency of side effects when scopolamine is given in doses necessary for a central depressant effect (0.6 mg and above). Side effects which can be seen with scopolamine hydrobromide in doses of 0.6 mg and above, orally, are dryness of the mouth, blurred vision, photophobia, and cardiac irregularities. Occasionally, constipation, urinary retention, hypersensitivity reactions, acute glaucoma, excessive restlessness and toxic psychosis can be seen. Infants, young children, and old people are especially susceptible to higher doses of the drug (Refs. 3 and 4). Doses of 2.0 mg orally in man often produce psychotomimetic effects (Ref. 24). On the basis of this toxicity, the Panel concludes that doses high enough to be effective as a nighttime sleep-aid would not be safe.

(2) *Scopolamine aminoxide hydrobromide.* There are products presently on the OTC market promoted for sleep which contain 0.125 to 0.5 mg of scopolamine aminoxide hydrobromide per unit dose, as part of a combination of ingredients. The Panel concludes that this ingredient is not effective as a nighttime sleep-aid in doses presently marketed, and that at higher, possibly more effective doses it would not be safe.

While the Panel is aware of some animal studies relating to the safety of scopolamine aminoxide hydrobromide, the literature on this ingredient is not voluminous and, in fact, the Panel has been unable to locate any documented evidence for the safety of this ingredient in humans. Even though the Panel is aware that scopolamine compounds have been marketed for over 50 years and that the OTC drug review procedures relating to safety (21 CFR 330.10(a)(4)(i)) provide for consideration of marketing experience, the Panel finds that such information is insufficient to support safe use of scopolamine at levels that would be effective as OTC nighttime sleep-aids.

The therapeutic value of scopolamine aminoxide hydrobromide is due to its metabolism in the body to scopolamine. The claimed reduction in toxicity compared to that of scopolamine hydrobromide may be due to the slow conversion of scopolamine aminoxide hydrobromide to the parent base, so that a sustained action is seen with few toxic effects (Ref. 10). Since there are no clinical studies in the literature on the scopolamine base substance alone, the usual way to discuss scopolamine aminoxide hydrobromide has been to compare it with scopolabine hydrobromide, for which there are experiments reported in the literature. Therefore, all of the previous discussion on scopolamine hydrobromide (pharmacology, toxicity, side effects, etc.), would be applicable here.

The Panel has been unable to locate any reports of controlled clinical studies on the effectiveness of scopolamine aminoxide hydrobromide alone as a nighttime sleep-aid in the recommended doses of 0.125 to 0.5 mg. An old (1927) French thesis by Lados, cited by Scharf (Ref. 10), reported on the effects of scopolamine aminoxide hydrobromide in 16 cases of postencephalitic parkinsonism. Lados claimed that scopolamine aminoxide hydrobromide, in earlier experiments with dogs, was 1/200 as toxic as scopolamine, and proceeded to use doses of 4.0 mg of scopolamine aminoxide hydrobromide per day with no toxic symptoms in patients with parkinsonism. Scharf himself (Ref. 10) used scopolamine aminoxide hydrobromide in doses of 2.0 mg/day to treat patients with parkinsonism, with no toxic effects. On the other hand, doses of 2.0 mg 3 times a day of scopolamine aminoxide hydrobromide do produce a significant number of side effects (nightmares, blurred vision, dry mouth, tinnitus or ringing in the ears) when given for seasickness (Ref. 25). These authors noted that 2.0 mg of scopolamine aminoxide hydrobromide "produced far more severe reactions than had 0.75 mg of scopolamine hydrobromide". They stated that in these doses the toxicity and duration of action of scopolamine aminoxide hydrobromide were at least as great as those of scopolamine hydrobromide. A more recent paper, in which antimotion sickness drugs were reviewed (Ref. 26), indicates that scopolamine aminoxide hydrobromide 2.0 mg and scopolamine hydrobromide 0.6 to 1.0 mg have similar actions, toxicities, and durations of action.

Another old paper (1945) by Co Tui and Debruille (Ref. 27) states that copolamine aminoxide hydrobromide is ⅓ as potent and ⅙ as toxic as scopolamine hydrobromide, and that in equipotent doses the effect of scopolamine aminoxide hydrobromide seems to last only ⅓ as long as that of the nonaminoxide compound. However, these conclusions were drawn on the basis of lethal dose studies in mice and abolition of the acetylcholine depressor effect on the blood pressure of the cat, and are difficult to extrapolate to man. Most importantly, the literature regarding the toxicity and effectiveness of scopolamine aminoxide hydrobromide appears to be too sparse and inconsistent to substantiate the routine use of this derivative in an OTC product. If it is assumed from Co Tui and Debruille's (Ref. 27) animal studies, for example, that scopolamine aminoxide hydrobromide is ⅙ as toxic and ⅓ as effective as scopolamine hydrobromide, then in equipotent doses scopolamine aminoxide hydrobromide becomes only ½ as toxic as scopolamine hydrobromide; therefore, the safety is still questionable. Furthermore, clinical studies have not confirmed this reduced toxicity of scopolamine aminoxide hydrobromide.

Although these early uncontrolled studies in animals suggested that scopolamine aminoxide hydobromide is less toxic than other scopolamine salts, most newer reports conclude that scopolamine aminoxide hydrobromide and scopola-

mine hydrobromide have similar actions, toxicities, and durations of action in doses of about 2:1, aminoxide hydrobromide to hydrobromide (Ref. 28). On the basis of the toxicity associated with scopolamine aminoxide hydrobromide, the Panel concludes that doses high enough to be possibly effective as nighttime sleep-aids would have toxicity similar to that of scopolamine hydrobromide, and that these doses would not be safe. Because of the inherent safety issues, the Panel concludes that further studies with scopolamine would be fruitless.

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c. *Miscellaneous compounds*—(1) *Acetaminophen, aspirin, salicylamide.* The Panel has been unable to locate any evidence that these ingredients are effective nighttime sleep-aids. The drugs have been referred to the Panel on Internal Analgesics for an opinion on their analgesic effects.

(2) *Passion flower extract, thiamine hydrochloride.* The Panel could find no valid scientific data to support the use of these ingredients as nighttime sleep-aids. After a search of the literature, the Panel was unable to identify a role for either passion flower extract or thiamine hydrochloride in the central nervous system in inducing sedation. Therefore, these ingredients were classified by the Panel as irrational (IR) for use in nighttime sleep-aid products.

*Labeling*

The Panel concludes that the following labeling claims are misleading and should be removed from OTC labeling: "natural sleep, normal sleep, refreshing sleep, sound sleep." These terms are misleading when these drugs are taken, since A drug is an exogenous, non-naturally occurring agent introduced into the body. Terms such as "non-habit-forming and guaranteed (fast acting)" are also misleading and probably false because it is very hard to prove that any product with psychotropic activity can be non-habit-forming or that a drug can be guaranteed to be effective in all cases.

3. *Conditions under 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 to permit final classification of the claimed active ingredients and labeling listed below. The Panel believes it reasonable to provide 3 years for the development and review of such evidence.

*Active Ingredients*

*Antihistamines*

Diphenhydramine hydrochloride
Doxylamine succinate [2]
Methapyrilene fumarate
Methapyrilene hydrochloride
Phenyltoloxamine dihydrogen citrate [2]
Pyrilamine maleate

a. *Antihistamines.* Histamine is a chemical substance normally concerned with inflammatory responses to irritants or injury. In sensitized individuals, it is released in one or more target organs (especially skin and mucous membranes) causing allergic reactions such as itching, swelling, hay fever, asthma, etc. (Ref. 1).

The antihistamines, as their name implies, are a class of drugs useful in antagonizing these actions of histamine. They can also exert side actions, including both drowsiness and then stimulation, depending upon the dose (Ref. 2). The sedative action, commonly seen in allergic patients, may be the major effect observed with their use in nonallergic individuals. This has led to the introduction of its application as the primary effect of some antihistamines as OTC sleep-aids for a target population whose chief complaint is sleeplessness.

The mechanism by which antihistamines accomplish the blockage or antagonism is apparently a competitive inhibition of already released histamine, rather than an interference with the release itself (Ref. 3). Thus, the skin manifestations of histamine release, i.e., itch, flare, wheal, capillary permeability and edema, are all decreased by antihistamines, although the dosage varies with the potency of the compound used. For example, equivalent inhibition of histamine-induced skin wheals is produced in man by 25 mg of promethazine and 175 mg of pyrilamine (Ref. 4).

In the respiratory tract, rhinorrhea and bronchospasm are both decreased by antihistamines. Paradoxically, however, antihistamines themselves can cause bronchoconstriction in man, and they have been shown to cause contraction of isolated strips of guinea pig tracheal smooth muscle at concentrations in the usual antihistaminic therapeutic range (Refs. 5 and 6).

[2] Ingredient placed in Category III (MH) with a marketing hold until adequate safety and effectiveness data for use as a nighttime sleep-aid have been submitted to the Food and Drug Administration.

Apart from their specific antagonism to the actions of histamine, the antihistaminic drugs may also exert other effects, some useful, some undesirable. Stimulation of the central nervous system has been observed in some patients with focal cortical lesions, in whom small doses of antihistamines may cause electroencephalographic (EEG) activation and even frank seizures (Ref. 7). Excessive doses in any patient may cause restlessness, excitation, delirium tremors, and even convulsions (Ref. 2); depression of the central nervous system is also frequently observed with the use of antihistaminic drugs. When these drugs are used to block histamine, drowsiness is common with antihistaminic therapeutic doses, a characteristic which makes the use of these drugs possible as OTC nighttime sleep-aids.

Sedation is perhaps the most frequently reported side effect associated with the use of antihistaminic agents (Ref. 1). Its manifestations may vary from inability to concentrate, dizziness and incoordination, to deep sleep. The sedative effect can be hazardous in ambulatory patients whose daytime activities require mental alertness and motor coordination (e.g., driving an automobile); and the Panel believes that warnings of this hazard should be required on OTC labeling for products containing antihistamines. The sedative effect, of course, would become the primary indication when these drugs are marketed for use as OTC nighttime sleep-aids and; therefore, no such warning is required.

Antihistamines not only have the two primary indications discussed above, but also exhibit a number of other side effects and toxicities, many related to anticholinergic activity (Ref. 8).

Central and peripheral nervous system manifiestations of toxicity from the use of antihistaminic drugs may include dizziness, tinnitus (ringing in the ears), lassitude, incoordination, fatigue, blurred vision, double vision, euphoria, nervousness, irritability, insomnia, anxiety, disorientation, vertigo, confusion, delirium, hyper reflexia, tremors, muscle spasm, convulsions (especially in children) and coma (Ref. 9). Fatal or near fatal overdoses cause fixed, dilated pupils, muscular twitchings followed by convulsions, coma, circulatory collapse and respiratory failure. Convulsions may persist for 24 hours, coma for 2 days, but death rarely occurs later than 24 hours after ingestion, unless due to infection associated with agranulocytosis (Ref. 10).

Gastrointestinal manifestations may include loss of appetite, nausea, vomiting, epigastric distress, constipation or diarrhea.

Cardiovascular symtoms may include palpitations (i.e., irregularities of heart rate and/or rhythm), hypotension, headache or tightness of the chest. In the genitourinary system, increased urinary frequency and/or difficulty in urination may be encountered. Skin rashes and photosensitivity may occur. Hematologic complications, fortunately rare, include leucopenia, thrombocytopenia, hemolytic anemia and agranulocytosis. Depending upon dose response relationships, some antihistamines may actually liberate histamine or serotonin, thus possibly contributing to adverse reactions such as bronchospasm.

Most antihistamines have some anticholinergic (atropine-like, belladonna-like) activity (Ref. 8). The action is not usually intense enough to be of therapeutic significance, but this activity may account for dryness of the mouth seen in some patients and more rarely, for other dysfunctions such as difficulty in urination and impotence (Ref. 1). Tingling, heaviness, and weakness of the hands may also be observed. Overdoses may cause mammary gland enlargement in both sexes, with secretion of milk. This effect has been attributed to depression of the hypothalamus with release of lactogenic hormone (Ref. 10).

The Panel is aware that the differences in chemical structure of the various antihistamine groups will have a significant effect on the sleep-aid indication. The groups may be classified as follows (Ref. 11):

Ethanolamines (examples: diphenhydramine, doxylamine and phenyltoloxamine). The drugs in this group are potent and effective histamine antagonists that possess significant atropine-like activity and have a pronounced tendency to induce sedation. With conventional antihistamine treatment doses, about half of the individuals who are treated with these drugs experience drowsiness. The incidence of gastrointestinal side effects, however, is low in this group.

Ethylenediamines (examples: methapyrilene and pyrilamine). These too, are highly effective histamine antagonists. These agents do not have a strong central nervous system action and may not produce a therapeutic somnolence even though a fair number of patients will exhibit drowsiness. Gastrointestinal side effects are quite common. This group contains some of the oldest and best-known antihistamines.

Alkylamines (example: chlorpheniramine). Antihistamines in this group are among the most active histamine antagonists and are generally effective in relatively low doses. These agents are not so prone to produce drowsiness and may be among the more suitable agents for daytime use; but again, a significant proportion of patients do experience this effect. Side effects involving central nervous system stimulation are more common in this than in other groups.

Piperazines (example: chlorcyclizine). The oldest member of this group, chlorcyclizine, is a valuable histamine antagonist with prolonged action and comparatively low incidence of drowsiness. The others are used primarily to counter motion sickness. The incidence of untoward effects, both central nervous system depressant and atropine-like, seems to compare favorably with that of other antihistamines. The possibility of some dulling of mental alertness should be borne in mind when the subject may be called upon to perform exacting and potentially hazardous tasks, such as driving a car.

Phenothiazines (example: promethazine). Most drugs of this class are histamine antagonists. The prototype, promethazine, was introduced in 1946 for the management of allergic conditions. The prominent sedative effects of this compound and its value in motion sickness were early recognized. Promethazine and its many congeners are now used primarily for their central depressant properties.

The problem for all the antihistamines when used as nighttime sleep-aids, from the Panel's point of view, is to ensure that the dosage recommended (e.g., possibly 50 mg in the case of diphenhydramine hydrochloride) is adequate for the sedative effect desired, yet not so large that toxic effects (see discussion below) result. The Panel is also concerned that, in currently available antihistamine OTC products promoted for sleep, dosages may have been reduced by the manufacturer to borderline or ineffective levels to avoid toxicity. The Panel feels that higher doses as recommended below by the Panel should be studied for some antihistamines to be used as nighttime sleep-aids.

Except for methapyrilene and pyrilamine, the Panel is unaware of any products containing antihistamines promoted for sleep on the OTC market. As indicated above, it is the opinion of the Panel that these two ingredients are currently used as OTC sleep-aids at very low doses; and therefore, the Panel was unable to find sufficient information on these or any other antihistamines which would allow the Panel to make a determination that they should be generally recognized as safe and effective for OTC use. Until such time as these data are available to the Food and Drug Administration, the Panel recommends that these ingredients be placed in Category III, with an additional period of 3 years for testing.

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(1) *Diphenhydramine hydrochloride.* The Panel concludes that clinical experience with diphenhydramine hydrochloride as a prescription drug for use as an antihistamine agent strongly suggests that in an appropriate dosage (50 mg to a maximum 100 mg single dose at bedtime) it may be effective as an OTC nighttime sleep-aid. The ingredient is currently not marketed for any indication in an OTC product. Physicians have used diphenhydramine hydrochloride as a sleep-aid for many years because of its sedative side effects. However, only a few studies exist for the sleep indication and therefore the Panel has determined that further testing in well-controlled studies is required to assure the safety and effectiveness of the suggested dosage of 50 to 100 mg single dose at bedtime. (See paragraph II D below—Data Required for OTC Nighttime Sleep-Aid Ingredient Evaluation). The Panel realizes that diphenhydramine is not currently available for OTC use, but because of well-established and documented safe clinical use for many years as described in the discussion below, the Panel has classified the ingredient in Category III.

Available evidence suggests that doses of 25 mg are ineffective (Refs. 1, 2 and 3). However, EEG studies with 25 and 50 mg doses indicate sedation, especially with the larger dose (Ref. 4). Doses of 50 mg or more have been reported to be as effective as doses of 100 mg or more of secobarbital or pentobarbital (Refs. 5, 6, 7, 8 and 9). Additional (minimum of three) well-controlled studies are required to determine whether diphenhydramine in doses of 50 mg is both effective and sufficiently safe to permit its use as an OTC nighttime sleep-aid.

Diphenhydramine was the first antihistamine produced in this country (Ref. 10). It is described (Ref. 11) as a potent antihistamine with a high incidence of sedation, mild antitussive effects, antiemetic effectiveness equal to dimenhydrinate, and is the antihistamine of choice for parenteral use in treatment of anaphylactic reactions.

Based on a review of this drug by the National Academy of Sciences-National Research Council (NAS/NRC), it was classified as "probably" effective for the sedation indication as follows: "For intractable insomnia and insomnia predominant in certain medical disorders." That group recommended that final classification required further investigation (Ref. 12).

The sedative properties of diphenhydramine have been exploited by anesthesiologists as a useful adjunct to preoperative medication (Refs. 13 and 14). The sedative action of diphenhydramine has been utilized in obstetric patients during labor (Ref. 15) and in the preoperative preparation of surgical patients (Ref. 13). Sedation determined by EEG examination was reported in one laboratory study (Ref. 4), while effectiveness in producing sleep was verified in two other EEG laboratories (Refs. 5 and 21) and also in a comprehensive drug surveillance program (Refs. 6 and 9).

Curiously, although antihistaminic drugs commonly produce drowsiness in patients, this effect is not observed in animals receiving comparable doses (Ref. 16). Therefore, a suitable animal model to test the sedative effect of new antihistaminic compounds in man does not exist. However, Winter (Ref. 16) postulated that it is possible to demonstrate a sedative action of an antihistaminic drug in animals by giving the test drug in connection with administration of a drug of known sedative action. This was accomplished with diphenhydramine and other antihistaminics administered in doses in 10 mg/kg injected subcutaneously into mice, followed in ½ hour by intraperitoneal administration of hexobarbital 100 mg/kg. The mean (average) sleeping time was prolonged about 40 percent by diphenhydramine, from $39.3\pm1.4$ minutes to $56.4\pm1.9$ minutes. Similarly, diphenhydramine 10 mg/kg prolonged mean sleep time obtained with pentobarbital 50 mg/kg in mice from $36.0\pm0.86$ minutes to $53.8\pm0.86$ minutes. Comparable results were obtained using guinea pigs receiving diphenhydramine 10 mg/kg and hexobarbital 35 mg/kg. Sleep time was prolonged from 50 to 73 minutes. Other investigators (Refs. 17 and 18) have confirmed prolongation of barbiturate sleep as a valid method for demonstrating the sedative action of antihistaminic drugs in animals. It should be noted that the studies above demonstrate only prolongation of sleep and not a true potentiation of the sedative effect of the barbiturate used. For example, a subhypnotic dose of pentobarbital (25 mg/kg intraperitoneally) in mice was not converted to a sleep dose by the addition of diphenhydramine in doses of 12.5 to 100 mg/kg orally (Ref. 3).

The sedative effect of diphenhydramine, alone or in combination, has been evaluated in a variety of ways. Sachs (Ref. 19) found it the major side effect in a series of 1,210 patients receiving diphenhydramine.

Friedlander (Ref. 5) examined sleep EEG's of 48 patients receiving secobarbital 200 mg or diphenhydramine 100 mg by mouth (the first sleep was with secobarbital in 21 patients). Both drugs were equally effective in induction and maintenance of sleep. Minor differences in amount of abnormal brain activity of various types led Friedlander to the conclusion that, in the dosage given, diphenhydramine might be "a little better drug" than secobarbital for obtaining sleep EEG's.

In a study by Goldstein et al. (Ref. 4), EEG frequency analysis in 42 human volunteers receiving diphenhydramine in does of 25 or 50 mg revealed predominantly increased low amplitude activity (i.e., "low energy sedation"). Not surprisingly, the effect was more marked with the larger dose.

Noell et al. (Ref. 8) used more than 3,000 male volunteers in a carefully controlled daytime EEG study of 33 antihistamines, secobarbital and placebo. Diphenhydramine 50 mg ranked second among the antihistamines, after dimenhydrinate, in time to "end of wakefulness" and thirteenth in time to "onset of sleep"; it was significantly superior to placebo in both of these effects.

Jaattela et al. (Ref. 20) compared the effects of oral daytime administration of the tranquilizer diazepam 10 mg, diphenhydramine 50 mg and placebo (sodium lactate) on mood and psychomotor function in 270 healthy medical students 20 to 23 years of age, divided into three groups (65 men, 25 women). Both drugs decreased activity in men and women and caused some euphoria in men. Diphenhydramine had a slightly greater depressant effect than diazepam on mental functions (as determined by standard tests, e.g. Nowlis adjective check list, digit symbol test, ability to repeat numbers in series).

An abstract by Bjerver and Goldberg (Ref. 2) refers to the central depressant action of a number of antihistamine compounds, including diphenhydramine, without providing details.

The Panel reviewed three studies designed to evaluate the sedative-hypnotic effects of the ingredients methaqualone 250 mg and diphenhydramine 25 mg separately and together in combination. The combination was derived from the demonstrated potentiation of methaqualone by diphenhydramine in the laboratory (Ref. 21). The first study was conducted by Beaubien et al. (Ref. 1) on psychiatric in-patients who received unidentified capsules containing either the combination, methaqualone 250 mg or diphenhydramine 25 mg. The capsules were distributed at random to 18 patients in double-blind fashion for a total of 200 sleeps. Nurses and patients each rated induction and duration of sleep and presence or absence of morning drowsiness and sluggishness on a 4-point scale.

There was some indication that the combination is superior to either methaqualone or diphenhydramine in regard to sleep induction, while the combination and methaqualone alone are equal and both superior to diphenhydramine 25 mg in maintaining sleep.

In the second study, Bordeleau et al. (Ref. 22) compared the sleep produced during 5 consecutive nights by the combination (methaqualone 250 mg and diphenhydramine 25 mg), methaqualone 250 mg, diphenhydramine 25 mg, secobarbital 200 mg and placebo in 101 female psychiatric patients averaging 37.1 years (range 17 to 62 years). Results were evaluated with a questionnaire con-

cerning duration and quality of falling asleep, duration and quality of sleep itself and subjective state on awakening and during the morning. The two single hypnotics (methaqualone and secobarbital) and the combination were found significantly superior to diphenhydramine and the placebo in quality and duration of both falling asleep and sleep itself; it was impossible to differentiate diphenhydramine 25 mg from the placebo in any of the five parameters of sleep studied.

In a third study, by Norris and Telfer (Ref. 14), the sedative effectiveness of diphenhydramine 25 mg appeared more favorably. This again was a comparison of the sedative effects of methaqualone 250 mg and diphenhydramine 25 mg in fixed combination, the individual ingredients and placebo in 200 otherwise healthy female patients undergoing minor gynecologic operations. The patients were divided into groups of 50, handled in double-blind fashion. Although both the mean sedation score and the number of patients showing good sedation were higher after the combination than after diphenhydramine 25 mg, the differences were not satistically significant. Changes in heart rate and blood pressure were minimal after each of the drugs, and postoperative nausea and vomiting were rare.

Cappe and Pallin (Ref. 15), aware of the sedative side effects of antihistamine drugs, explored the extent of hypnosis and analgesia with dispenhydramine and chlorprophenpyridamine in obstetric patients during labor and delivery. Each drug was administered to 30 patients in fractional doses intravenously. Moderate analgesia was achieved in 35 to 40 percent of patients receiving diphenhydramine (30 to 120 mg) or chlorprophenpyridamine. Untoward effects included nausea and vomiting and drop in blood pressure, but not respiratory depression in the newborn.

In another study, Lear et al. (Ref. 13) compared the sedative effectiveness of preoperative medication with various tranquilizers in 1,159 surgical patients. They administered chlorpromazine 12.5 to 50 mg intramuscularly to 350 patients, mepazine 200 to 400 mg orally to 434, promethazine 25 to 50 mg intramuscularly to 193 and diphenhydramine 50 to 100 mg intramuscularly to 132, using as controls a mixed series of 262 patients who received either morphine or meperidine and a belladonna derivative with or without a barbiturate. All of the tranquilizers diminished undesirable reflex activity while causing less overall depression than with the narcotics and barbiturates. The incidence of postoperative nausea and vomiting was reduced, especially with chlorpromazine. Among the 182 patients receiving diphenhydramine, sedation was rated as nil in 15 percent, slight in 34 percent, moderate in 46 percent and marked in 5 percent.

The authors noted that diphenhydramine has been used clinically at bedtime for sedation, either alone or in combination with barbiturates, for the apprehensive patient. Occasionally it has replaced the barbiturates for sedation, even in the allergic patient. The authors further noted that diphenhydramine combined with meperidine is useful preoperatively for brief procedures requiring early ambulation such as vein ligations and for other forms of minor surgery such as dilatation and curettage, removal of simple breast tumors, and incision and drainage.

Two pertinent papers have emerged from a group headed by Jick and Slone, who have established a comprehensive drug surveillance program in three Boston hospitals. The first of these (Ref. 6) concerns a double-blind comparison in adult medical patients of three hypnotic drugs: chloral betaine 750 mg (equivalent to chloral hydrate 500 mg), diphenhydramine 50 mg, pentobarbital 100 mg and a placebo. Fifty bottles of each of the drugs and 100 of placebo were numbered randomly and assigned in numerical order to patients requiring hypnotics. Of the original 250 patients entered into the trial, 195 (86 males, 109 females) received one or more of the prepared capsules. The average age and weight of patients receiving one of the hypnotic drugs were 56.3 years and 70.8 kg, respectively, and of those receiving placebo were 53.7 years and 68.5 kg, respectively. Hypnotic effectiveness was rated by the physician as "good," "fair," "poor," or "don't know." Because 59 patients received a "don't know" rating, analysis of effectiveness was confined to the remaining 136 patients. Statistically, no differences were evident ($P=0.50$) among the hypnotic drugs but all were superior to placebo: ratings were "good" or "fair" in 17 of 24 patients receiving chloral betaine, 23 of 28 with diphenhydramine, 20 of 24 with pentobarbital and 28 of 60 with placebo.

The second report from this drug surveillance program (Ref. 9) concerns the clinical effects of four hypnotic drugs (chloral hydrate, diphenhydramine, secobarbital and pentobarbital) in 2,045 patients, each receiving one or more of the four drugs in treatment of insomnia. All four drugs were reasonably effective; but, unfortunately, no placebo was used. In the case of diphenhydramine, it is of interest to note that doses were 100 mg in 46 patients (9 percent) and 25 mg in 24 patients (5 percent). Adverse effects were reported in nine patients (1.8 percent) receiving diphenhydramine; of these, seven received 50 mg and two received 100 mg. Vomiting occurred in one case and central nervous system depression in eight, in one of whom depression was deemed "major." All of the patients recovered promptly when the drug was discontinued, and there were no complications.

Another study, by Teutsch et al. (Ref. 23), evaluated sleep following pentobarbital 100 mg, diphenhydramine 50 mg, methapyrilene 50 mg or placebo in 159 patients in two Veterans Administration Hospitals. They found both pentobarbital and diphenhydramine, but not methapyrilene, were significantly better than the placebo when evaluated by the subjective question, "How long did you sleep?" In one of the two hospitals, methapyrilene was superior to the placebo, while in the other hospital, it was not. The authors further state that these findings confirm the results of another comparison between pentobarbital and diphenhydramine which they conducted earlier in 110 patients.

Vogel et al. conducted a double-blind EEG study of the effect of diphenhydramine 50 mg on the sleep of six healthy adult volunteers with both subjective and objective insomnia (Ref. 24). Placebo controls were not used.

Significant changes were observed by Vogel. They included a decrease in sleep latency and an increase in total sleep time, the latter being mainly accomplished by a significant increase in stage 2 sleep; the drug had no effect on delta or deep sleep. There was a small but statistically significant rapid eye movement (REM) deprivation (significant reduction in duration of REM sleep and increase in REM latency, with an almost significant REM rebound). There were no significant changes in subjective sleep variables, nor were important side effects encountered. Slightly more than base line drowsiness was reported by four of the six subjects the next morning, by two subjects on three and six mornings, respectively, following drug administration and by one subject one evening. It was concluded that diphenhydramine 50 mg significantly decreased EEG latency and increased duration of EEG sleep without significant side or toxic effects.

Diphenhydramine has been classed as a potent antihistamine with a high incidence of sedation (Ref. 11). The data in the present reports are confirmatory and suggest that a useful sedative-hypnotic effect may be obtained with diphenhydramine in doses of 50 to 100 mg. Diphenhydramine hydrochloride 25 mg, the amount contained in a combination preparation previously described (Ref. 14), is much less effective than the other constituent, methaqualone 250 mg.

With reference to safety, available data (Ref. 25) indicate a definite but low order of toxicity, unless dosage exceeds 100 mg. Instances of poisoning, accidental or suicidal, have been reported with diphenhydramine. Toxic psychoses from overdose of the drug have been observed (Ref. 26). Possibly the earliest suicide was that reported by Duerfeldt in 1947 (Ref. 27). Wyngaarden and Seevers (Ref. 28) listed a 6-month-old child who died in convulsions and a group of adults, ranging from 18 to 72 years in age, who sustained nonfatal convulsions, excitation, toxic psychosis, coma, petit mal or somnolence. These are typical examples, rather than a complete compilation.

Also of interest are observations that diphenhydramine is an enzyme inducer, i.e., it stimulates the activity of microsomal enzymes in the liver which metabolize a variety of drugs (Refs. 29, 30, 31 and 32). Examples of drugs whose metabolism in the body is so accelerated are zoxazolamine (Ref. 29), aminopyrine

(Ref. 31), carisoprodol (Ref. 30), some oral anticoagulants, barbituarates, corticosteroids, diphenylhydantoin, griseofulvin and diphenhydramine itself (Ref. 27). Since enzyme induction requires repeated use of the inducing drug, this problem would ordinarily not occur with OTC preparations intended for occasional use.

The Panel concludes that evidence already at hand strongly suggests that diphenhydramine in an appropriate dosage (50 mg single dose at bedtime) could prove effective as an OTC nighttime sleep-aid. The Panel recommends that diphenhydramine be made available as an OTC nighttime sleep-aid in a maximum 50 mg single dose at bedtime. Diphenhydramine has therefore been placed in Category III with 3 years provided for testing during which the ingredient may be clinically investigated at doses up to 100 mg to establish the minimally effective dose.

In addition, because past experience has shown that many nighttime sleep-aids have been misused and since there is no experience in the OTC market with this ingredient, the Panel believes that the quantity of the drug available in a product container should be limited to prevent accidental ingestion of a lethal dose.

The Panel believes that reported observations of anticholinergic and other side effects cannot be overlooked and need to be evaluated. Should such side effects prove not serious in a minimum of three additional well-controlled positive studies for the labeled claim of clinical effectiveness, the drug categorization may be changed from Category III to I.

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(2) *Doxylamine succinate.* The Panel concludes that, in an appropriate dosage (25 to a maximum 50 mg single dose at bedtime), doxylamine succinate may be both safe and effective as an OTC nighttime-sleepaid, but further evidence of safety and effectiveness is needed. This drug is presently marketed as an antihistamine available by prescription in doses of 12.5 to 25 mg 3 to 4 times a day for adults, or 6.25 mg 2 to 4 times daily for children under 12 years and also available OTC as an antihistamine in doses of 3.75 to 7.50 mg 3 to 4 times a day for adults or 3.75 mg 4 times a day for children under 12 years.

Then Panel has placed the ingredient in Category III (MH) with a restriction on marketing since it is not currently marketed as an OTC nighttime sleep-aid, and further testing is required to demonstrate its safety and effectiveness for this indication. The Panel understands that the Agency can place this ingredient in Category II instead of Category III (MH) which has the effect of prohibiting marketing until an approved new drug application (NDA) is obtained or until the OTC nighttime sleep-aid monograph is amended to include the ingredient.

In antihistaminic sedative potency, doxylamine succinate resembles other antihistamines in the ethanolamine class. One paper (Ref. 1) indicates that doxylamine succinate is a potent antihistamine which shows a high incidence of sedation with average therapeutic doses. Feinberg (Ref. 2) grades the sedation of 12.5 mg of doxylamine succinate the same as that of 25 mg of methapyrilene hydrochloride, while other researchers contend that the sleep-inducing effect of doxylamine is significantly greater than that of methapyrilene (Ref. 3).

The exact mechanism of central nervous system depression by doxylamine is unknown, and there is nothing in the literature on the absorption and fate of doxylamine in humans. In male rats, 7 to 21 percent of a single intravenous or oral dose of the succinate is excreted in the urine within 24 hours of administration, while in female rats the amount excreted is 17 to 30 percent (Ref. 4). Dogs receiving daily oral doses of doxylamine

[3] Cited OTC Volumes refer to the submissions made by interested persons pursuant to the call for data notices published in the FEDERAL REGISTER of August 22, 1972 (37 FR 16885) and May 25, 1973 (38 FR 13763). 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.

succinate for prolonged periods consistently eliminate about 20 percent of the daily dose in the urine. Snyder and coworkers (Ref. 4) concluded, on the basis of tissue determinations of the drug and urinalysis of excreted products, that the bulk of the administered drug is metabolized in the body.

Brown and Werner (Ref. 1) found the intravenous $LD_{50}$ (defined as a dose that is lethal for 50 percent of the test animals) for doxylamine succinate to be 49 and 62 mg/kg for rabbits and mice, respectively. Subcutaneously in mice and rats or orally in mice, the compound was about ⅛ as toxic as when given intravenously. It was about ⅕ as toxic orally in rabbits. In mice and rats, acute toxicity was similar for both sexes. They also found favorable ratio of effectiveness to toxicity for guinea pigs.

Acute toxicity studies in dogs showed that oral doses of 7.5 mg/kg of doxylamine succinate produced no evidence of toxicity (Ref. 5). Repeated administration of 15 mg/kg 3 times a day caused some loss of appetite and weight, mydriasis, apprehension, and muscular tremors in three out of four dogs. Similar effects occurred in one of two monkeys at dose levels of 16 to 20 mg/kg 3 times daily. Lower doses produced no such toxic effects.

In the same studies, 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, as judged by gross signs of toxicity, hematologic determinations, and histopathology. 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 anorexia and death, in one case. Thus repeated doses resulted in toxicity only when the doses approached acutely lethal ones.

In a test for teratogenic effects of a combination of doxylamine and dicyclomine (a product used for treating nausea of pregnancy), doxylamine succinate was given orally to rabbits in doses of 10 to 100 mg/kg/day (Ref. 6). Neither doxylamine, dicyclomine nor the combination had any deleterious effects on pregnancy maintenance, litter size or fetal weight in the rabbit, except when maternal toxicity was produced. In rats, the same doses produced no alteration in breeding, conception, pregnancy maintenace, litter size or fetal weight, although a dose-related decrease in body weight gain did occur in rat pups from doxylamine and and dicyclomine-treated mothers.

Feinberg and Bernstein (Ref. 7) found that in 118 patients being treated for allergy with doses of 12.5 to 25 mg of doxylamine succinate, side effects were observed in 39 of them. Sedation or sleepiness was seen in 36 of the 39 patients. 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.

Keeney (Ref. 8) states that the use of doxylamine succinate as an antihistamine is infrequently followed by side effects, but MacQuiddy (Ref. 9) says that such side effects are "quite frequent" with the 50-mg dose of doxylamine succinate although with the 25-mg dose the number of reactions decreases "materially," while clinical results remain satisfactory. MacQuiddy concludes that doxylamine succinate is a safe and effective medication, having seen no reactions of any severity during his clinical study, with principally drowsiness and occasionally nausea being the main side effects.

Sheldon et al. (Ref. 10) gave allergic patients 12.5 to 200 mg of doxylamine succinate and found that 57 percent complained of drowsiness. However, the authors noted no apparent correlation between the dosage of the drug and drowsiness. Palpitations, irritability, and diarrhea were noted in three separate instances. There was no evidence of any hepatic, renal or vascular changes.

Finally, Ferguson (Ref. 11) gave schizophrenic patients up to 1,600 mg of doxylamine succinate daily by mouth for up to 6 months and found few side effects. He evenremarked about the lack of sedation or drowsiness with high doses, noting that a combination of 900 mg doxylamine and 270 mg of phenobarbital daily produced no sedation, whereas 270 mg of phenobarbital alone produced an all-day sleep, therefore suggesting even an antagonism of phenobarbital's hynotic effect by doxylamine. There were no changes in pulse, respiration, temperature or blood pressure with the high doses used in Ferguson's study, and blood chemistry and organ function tests remained normal, yet the doses were encouragingly effective in treating schizophrenic patients. In addition, after giving doxylamine to schizophrenics, Ferguson found "there has been no habituation to doxylamine, but a mild degree of tolerance has been noted." He indicated that during a 6-month period, the dose had to be increased in some patients from 300 to 900 mg daily to maintain satisfactory results. Partially confirming these data was the work of Selzer and Waldman (Ref. 12), who gave chronic psychotic patients doses of doxylamine (unspecified salt) up to 900 mg/day for 3 months. Side effects were also virtually nonexistent in this study.

There were only a few citations found in the literature for tolerance buildup to the sedative effects of antihistamines, and all of these are unsubstantiated.

Thompson and Werner (Ref. 5), for example, state in their toxicity experiments that repeated administration of doxylamine succinate to rats in large doses for a comparatively long period did not lead to tolerance or accumulation. However, Feinberg (Ref. 2) states that there is a definite tendency for the rapid development of tolerance to the sedative effects of (all) antihistamines.

Since the depressant actions of antihistamines are additive with the effects of other central nervous system depressants, the concomitant use of alcoholic beverages or other drugs known to depress the central nervous system should be avoided (Ref. 13). Brown (Ref. 14) says that such combinations produce deepened and prolonged sleep.

It appears from some studies that 50 mg and above of doxylamine succinate produces the side effect of sedation when the drug is used as an antihistamine (Refs. 7 and 14). 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 schizophrenic patients. Such apparently contradictory results need to be explained.

No literature was found concerning poisoning or doses which cause death in humans.

Acute toxicity studies in animals which have been reported make no mention of the behavior of the animals before death, except that they died in convulsions. Chronic toxicity studies (Ref. 5) mention that dogs appear "apprehensive" after 15 mg/kg of doxylamine succinate 3 times daily, and that a monkey given 20 mg/kg 3 times daily yawned frequently, was apprehensive, and upon handling exhibited convulsive tremors.

The drowsiness effect of doxylamine in humans, as with other antihistamines, is well documented (Ref. 2). As mentioned earlier, doxylamine is a potent antihistamine with a high degree, compared with other antihistamines, of central nervous system depression as well. It may be stimulatory at higher doses, as suggested by the chronic toxicity studies in dogs and monkeys.

Only two clinical reports on the effectiveness of doxylamine as a sleep-aid have been found. The first study, by Noell et al. (Ref. 15), was performed on more than 3,000 men for the purpose of evaluating the sedative effects of over 20 antihistamines by electroencephalographic (EEG) methods and comparing these effects with those of barbiturate and nonbarbiturate hypnotics. Doxylamine succinate 25 mg was one of the three most sedating antihistamines, producing a significantly reduced latency to end of wakefulness, and comparing favorably with established hypnotic drugs such as secobarbital and pentobarbital in sedation activity. It was chosen as the antihistamine based on dosage causing the earliest onset of sleep.

The second study, by Sjoqvist and Lasagna (Ref. 3), compared the effectiveness of 25 and 50 mg of doxylamine succinate as a nighttime hypnotic with that of placebo and two doses of secobarbital. Both drugs were shown to be significantly better than placebo, and both doses of doxylamine scored better than 100 mg of secobarbital but not as well as 200 mg of secobarbital. There were few side effects, other than hangover, with both drugs. Two weaknesses of the study were (1) the high placebo effect (50 percent of the patients slept as well on placebo as on their previous hypnotic medication) and (2) the lack of a dose-related difference in effectiveness between the two doses of doxylamine used.

Both of the above-mentioned studies suggest that doxylamine may have nighttime sleep-aid potential.

In summary, the Panel notes that the potential effectiveness of doxylamine succinate as an OTC nighttime sleep-aid is shown by the fact that there were 33 percent side effects (primarily sedation or sleepiness) in one study where individual doses of up to 50 mg were used for the treatment of allergy (Ref. 7). No serious side effects were noted after use of the drug for 6 months. The Panel notes that studies in which high doses (up to 1,600 mg/day) of doxylamine succinate were given to schizophrenic patients (Ref. 11) suggest that the drug is relatively safe. However, it is possible that psychotic patients do not respond to high doses of centrally active drugs in the same manner as nonpsychotic individuals.

The Panel concludes that since the ingredient is not currently marketed as an OTC sleep-aid, it should be placed in Category III (MH) with a marketing hold during the testing period provided. The Panel concludes that the available reports on the safety of doxylamine succinate are not adequate to permit its use as an OTC nighttime sleep-aid. The Panel recommends that a minimum of five additional well-controlled studies are necessary to establish the safety and effectiveness of the ingredient as an OTC nighttime sleep-aid. At least two EEG studies and at least three clinical studies are necessary. The Panel has determined that an appropriate dosage for testing should be limited to 25 to a maximum 50 mg single dose at bedtime.

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(3) *Methapyrilene hydrochloride and methapyrilene fumarate.* The Panel concludes that methapyrilene hydrochloride and methapyrilene fumarate are probably safe and may be effective as OTC nighttime sleep-aids in appropriate dosages (25 to a maximum 100 mg single dose at bedtime). The Panel considers it feasible to handle both salts of methapyrilene (hydrochloride and fumarate) as similar drugs because their molecular weights are in the ratio of 1(base):1.1 (hydrochloride):1.5(fumarate). Most studies have been performed with the hydrochloride salt whose weight is close to that of the base. The ingredients are currently marketed as OTC sleep-aids which contain 10 to 26 mg per tablet or capsule, except one which contains 50 mg. The Panel notes that the recommended dosage of the various OTC preparations (25 to 50 mg) is substantially below the 100 mg dose at which patients receiving the drug for various allergies experienced drowsiness (Ref. 1). There is some evidence of effectiveness at a bedtime dose of 50 mg (Refs. 2 and 3) but others report drowsiness only at 100 mg (Ref. 1). The Panel has placed the ingredients in Category III since it has insufficient information on the safety and effectiveness of these active ingredients. The Panel has determined that further testing in well-controlled studies is required to assure the effectiveness of the suggested dosage of 25 to a maximum 100 mg single dose at bedtime. (See paragraph II D below—Data Required for OTC Nighttime Sleep-Aid Ingredient Evaluation.)

Methapyrilene was introduced clinically by Feinberg and Bernstein 1 year after diphenhydramine (Ref. 4). Its antihistaminic and antianaphylactic activity was verified in experimental animals and its antiallergenic activity documented in a varied series of 253 patients, whose average dose was 50 mg orally 1 to 4 times daily; a few patients received 100 mg doses, but these were frequently not well tolerated. In this apparently uncontrolled study, side effects were noted in approximately 25 percent of the patients. Sedation was the most common side effect, occurring in 48, or 19 percent, of the patients studied. The degree of sedation was not as great as that produced by diphenhydramine, but equaled or exceeded that of tripelennamine.

Kierland and Potter (Ref. 5) compared methapyrilene with diphenhydramine and tripelennamine in 126 dermatologic patients. Doses, given 3 or 4 times daily, were usually 100 mg of methapyrilene and 50 mg of the other two drugs. Improvement was comparable with the three drugs. Drowsiness was observed in 10 of the 126 patients receivng methapyrilene, 3 of 47 with diphenhydamine and 1 of 44 with tripelennamine, although the authors noted that the degree of drowsiness was more marked with diphenhydramine than with either of the other drugs.

The Friedlanders (Ref. 1) also verified antiallergic effectiveness of methapyrilene in 85 of 117 patients. Dosage was usually 100 mg 4 times daily for adults and 25 to 50 mg daily for children. One or more side effects, generally mild, occurred in about 25 percent of the patients, usually at the 100-mg (adult) dose level, and were frequently obviated by reduction in dosage to 50 mg. Of special interest was that drowsiness was observed in 19, or 16 percent, of the patients studied.

The classic paper on the hypnotic efdence of methapyrilene, offered in evidence for its effectiveness as a nighttime sleep-aid, is the study of Straus et al. (Ref. 2). In that study the authors compared 50 mg of methapyrilene with 100 mg of phenobarital and placebo under double-blind conditions in 54 male insomniac patients in a Veterans Administration hospital. The experimental design called for each patient to receive each medication 6 times for a total of 18 nights in 3 weeks (a few nights were missed). Drug administrations were randomized, except that no drug succeeded itself. Evaluations of effectiveness were objective (graded by nurses observing the patients hourly during the night) and subjective (as reported by the patients to a physician the next day) reports of three criteria: falling asleep (sleep latency), staying asleep and overall evaluation. A 4-point scale was used, ranging from 0 (no sleep response) to 3 (excellent sleep response). The data indicate that both methapyrilene and phenobarital were more efficient than placebo in their hypnotic effect. The nurses' observations found methapyrilene more effective than phenobarbital in inducing sleep (but the patients could not distinguish between the two compounds); in overall evaluation the patients favored phenobarbital (but the nurses could not differentiate between the two); and for staying asleep, neither patients nor nurses could distinguish between them. The authors concluded that the two drugs exerted approximately equal hypnotic effects, in each case significantly greater than that of the placebo. It should be noted that phenobarbital, with its known slow onset of

action, is not the ideal barbiturate hypnotic; secobarbital or pentobarbital would have been better choices for comparison. Nevertheless, the study does provide data demonstrating hypnotic effectiveness of methapyrilene in 50-mg doses.

In another study, Shapiro (Ref. 6) used methapyrilene from 1 to 66 days as a sedative in 33 hyperactive children ranging in age from 4 weeks to 12 years. The drug produced sleep and relaxation of hyperactive states during the daytime in 24 of 31 children, with nausea in one only. Nowhere in the article is the dosage defined.

Noell et al. (Ref. 7), in a daytime EEG study with over 3,000 Air Force volunteers, found that, of 33 antihistamines studied, methapyrilene 50 mg ranked eighteenth in time to "end of wakefulness" and fifth in time to "onset of sleep." In both of these effects methapyrilene scored significantly better than placebo but not nearly as well as secobarbital 100 mg.

Feinblatt and Ferguson (Ref. 3) compared methapyrilene niacinate, methapyrilene hydrochloride and placebo in a double-blind study involving 53 patients with insomnia. The dose of each methapyrilene salt was 50 mg (calculated as methapyrilene base). Both were considerably more effective than placebo, inducing "satisfactory sleep" in 37 (70 percent) of the 53 cases, "partial relief" in 9 (17 percent) and failing in 7 (13 percent).

More recently, Teutsch et al. (Ref. 8) used subjective responses to evaluate sleep following pentobarbital 100 mg, diphenhydramine 50 mg, methapyrilene 50 mg or placebo in 150 patients in two Veterans Administration hospitals. The four preparations, in identical capsules, were administered by a nurse-observer on each of 4 consecutive nights of a randomized program. Next morning the patients reported to the nurse how well they had slept, the time taken to fall asleep, how long they had slept, and how the sleep compared with their usual night's sleep at home. For all response variables, both pentobarbital and diphenhydramine were found significantly better than placebo when evaluated by the subjective question, "How long did you sleep?" In one of the two hospitals, methapyrilene was superior to placebo while in the other hospital it was not.

The Panel is aware of instances of poisoning, either accidental or suicidal, with methapyrilene. For example, fatalities have included a 15-month old girl who developed hyperpyrexia, cerebral edema, upper nephron nephrosis and uremia (Ref. 9) and an adult suicide who died in convulsions (Ref. 10). Examples of nonfatal cases include a 20-month-old child (Ref. 11) and two adults (Ref. 12), all manifesting convulsions, and a pregnant female with a toxic psychosis mimicking eclampsia (Ref. 13).

The Panel has also reviewed a number of additional studies in which methapyrilene was used in combination with salicylamide and scopolamine (Ref. 14). The Panel concludes that the weight of evidence is clearly in the direction of a positive effect: methapyrilene in these combinations almost certainly is able to produce drowsiness, EEG shifts, and reduced sleep latency. Since the effects are probably present but not strong with 50 mg of methapyrilene and since this appears to be a relatively safe drug, doses of 75 mg or 100 mg seem worth exploring (Ref. 14).

On the basis of evidence presently at hand, the Panel concludes that methapyrilene hydrochloride or methapyrilene fumarate in dosages of 25 to a maximum 100 mg in a single dose at bedtime may be effective as an OTC nighttime sleep-aid. The Panel recommends that a minimum of five additional well-controlled studies are necessary to establish the safety and effectiveness of the ingredient as an OTC nighttime sleep-aid. At least two EEG studies and at least three clinical studies are necessary. Should anticholinergic or other side effects prove not serious in these additional studies and should these studies in dosages of 50 mg and possibly up to 100 mg prove methapyrilene to be effective, i.e., significantly better than placebo in improving sleep in one or more sleep parameters, this drug could be moved from Category III to Category I.

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(14) OTC Volume 050043.[3]

(4) *Phenyltoloxamine dihydrogen citrate.* The Panel concludes that in appropriate dosage (100 to a maximum 200 mg single dose at bedtime), phenyltoloxamine dihydrogen citrate may be both safe and effective as an OTC nighttime sleep-aid, but further evidence of safety and effectiveness is needed. This drug is available on an OTC basis in a dose of 30 mg as an ingredient in a combination analgesic calmative preparation.

Phenyltoloxamine (also called phenoxadrine), one of the ethanolamine group of antihistamines, is also marketed in OTC combination products (22–89 mg of the dihydrogen citrate salt) for the treatment of bronchial asthma, allergic coryza, allergic cough, headache and other pain, and gastric hyperacidity due to nervous tension.

The Panel has placed the ingredient in Category III (MH) with a restriction on marketing since it is not currently marketed as an OTC nighttime sleep-aid, and further testing is required to demonstrate its safety and effectiveness for this indication. The Panel understands that the Agency can place this ingredient in Category II instead of Category III (MH) which has the effect of prohibiting marketing until an approved new drug application (NDA) is obtained or until the OTC nighttime sleep-aid monograph is amended to include the ingredient.

Phenyltoloxamine is a potent histamine antagonist, and the early literature on this drug stresses its apparently low acute and chronic toxicity. Extensive clinical studies have provided evidence that the drug is effective in relieving vasomotor rhinitis, hay fever, pruritis, eczema, urticaria, asthma, and certain allergic drug reactions (Ref. 1). Like other antihistamines, the drug has distinct local anesthetic properties and some antispasmodic activity. In addition, LaVerne (Ref. 2) lists the following properties without documentation: autonomic suppressant, adrenergic stimulant sedative, mild hypnotic effect, and no adverse effect on mental acuity. After the 1957 report by Sainz (Ref. 3) on the effects of the drug on psychotic patients, phenyltoloxamine achieved the reputa-

[3] Cited OTC Volumes refer to the submissions made by interested persons pursuant to the call for data notices published in the FEDERAL REGISTER of August 22, 1972 (37 FR 16885) and May 25, 1973 (38 FR 13763). 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.

tion of being a "phrenotropic" or tranquilizing drug. A number of reports then appeared on its therapeutic usefulness as a sedative (Refs. 4, 5 and 6).

The side effects of phenyltoloxamine are apparently mild in therapeutic doses, soporific (sleep-inducing) effects are low and occur in less than 7 percent of patients (Ref. 7).

In general, the mechanism of central nervous system depression by phenyltoloxamine is unknown, although a report by DeSalva and Oester (Ref. 8) suggests that phenyltoloxamine acts similarly to mephenesin and morphine sulfate in depressing polysynaptic reflexes in cats. Such a test has traditionally been used for studying central muscle relaxant activity, which may be indicative of sedative or tranquilizing potential.

The only study found concerning the absorption and fate of phenyltoloxamine was performed by Hoekstra et al. in 1953 (Ref. 9). Extrapolating from experiments performed in dogs, rats and mice for other purposes, they concluded that phenyltoloxamine is readily absorbed from the gastro-intestinal tract and peritoneal cavity and distributed rapidly throughout the body. Very little is known of its destruction, conjugation, or excretion, since attempts to isolate unchanged phenyltoloxamine or certain possible breakdown products from the urine of dogs were not successful. Hoekstra et al. (Ref. 9) also did acute toxicity studies in mice which compared the $LD_{50}$'s of phenyltoloxamine hydrochloride, phenyltoloxamine dihydrogen citrate, diphenhydramine hydrochloride and tripelennamine. Phenyltoloxamine hydrochloride was one-fifth as toxic intraperitoneally and one-twelfth as toxic orally as when given intravenously. It was one-half as toxic as tripelennamine and two-thirds as toxic as diphenhydramine hydrochloride when intraperitoneal $LD_{50}$'s were compared.

Acute toxicity studies of various doses of phenyltoloxamine in a few rats showed that oral doses greater than 680 mg/kg caused death preceded by hyperactivity, excitement, convulsions and respiratory depression. In dogs, intravenous doses above 20 mg/kg caused death, while lower doses produced ataxia, excitement followed by depression, and slight narcosis (Ref. 9).

Finally, limited chronic studies showed that dogs tolerate phenyltoloxamine dihydrogen citrate in daily oral doses of 20 and 40 mg/kg (calculated in terms of active moiety) with no untoward effects. There were no indications of blood dyscrasia at any time during the experiments (Ref. 9).

In general, clinical studies in man in which phenyltoloxamine has been evaluated as an antihistamine consistently show few side effects with doses of 25 to 50 mg of the dihydrogen citrate salt. Sainz (Ref. 3) performed a preclinical study in 48 patients to determine side effects and toxicity and found that mild drowiness appeared at oral doses above 200 mg 4 times a day, 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; and a slight blood pressure increase was seen. Doses higher than 200 mg 4 times a day 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 studies. Sainz concluded that the drug is not only safe but remarkably free from undesirable reactions at oral doses of 100 mg 4 times daily.

Cronk and Naumann (Ref. 10) gave 2,380 allergic patients with nonspecific upper respiratory infections 100 to 600 mg of phenyltoloxamine dihydrogen citrate daily and saw only three cases of side effects caused by the drug. These were manifested as a mild soporific state after 200, 300 and 600 mg of the salt, and in no case was the side effect severe enough to warrant discontinuation of the drug. Although this study suggests that the incidence of drowsiness with phenyltoloxamine is low, a later study by Fleischmajer et al. (Ref. 4) found a much higher incidence of central nervous system depression. Fifty patients received the drug (unidentified salt) for treating allergic cutaneous disorders in doses of 100 mg 3 times a day (after meals) and 200 mg at bedtime. In 39 patients (78 percent) there was excellent relaxation, lessening of inner tension, and improvement in the ability to sleep. Most of these patients noted a pleasant calmness within 30 to 60 minutes after taking the drug. The other side effects noted were blurred vision, vomiting, tachycardia, dry mouth, and marked hypnosis, but only 3 patients discontinued therapy because of the severity of these effects.

Finally, in a study designed to test the usefulness of phenyltoloxamine in chronic schizophrenics, Barsa and Saunders (Ref. 11) gave 60 female patients gradually increasing doses of phenyltoloxamine (unidentified salt), with the highest dose reached being 800 mg 4 times a day. The patients received the drug for 3 to 5 months. It was seen that when the dose was below, 1,600 mg per day, most of the patients were stimulated, becoming more alert, but also more restless and irritable. As the daily dose went above 1,600 mg, the excessive stimulation disappeared and the psychosis appeared to improve. However, most of the patients could not tolerate the high dose. Forty patients (67 percent) complained of nausea or loss of appetite: 10 of these also experienced vomiting. Fifty patients showed an average weight loss of almost 5 kg (11 lb). Other patients complained of generalized weakness, fainting, ataxia, parkinson-like symptoms, and generalized tremulousness. All of these side effects disappeared when the dosage was reduced. Hematological tests, liver function tests, and urinary studies showed no significant changes in any of the patients.

Few reports on tolerance to phenyltoloxamine were found in the literature. Cronk and Naumann (Ref. 10) mentioned in passing that at the end of their experiments considerable adaptation had apparently developed in that the sedation effect had become subjectively less severe after 200 to 600 mg of dihydrogen citrate salt per day for 3 days.

Although the Panel could find nothing in the literature on inteactions of phenyltoloxamine with other drugs, it is expected that, like other antihistamines, phenyltoloxamine could interact with central nervous system depressants.

The average oral antishistamine dose of the dihydrogen citrate salt for adults is 50 mg 3 to 4 times daily. This may be increased if the desired therapeutic response is not obtained or if side effects do not become pronounced (Ref. 7). In one study such doses produced a rather low incidence of drowsiness, around 7 percent (Ref. 7), but another study (Ref. 4) suggests a much higher incidence of central depression (78 percent), with higher doses (100 mg 3 times a day, unspecified salt). Single doses of 400 mg (unspecified salt) produced sedation and moderate hypnotic effect in 100 percent of healthy volunteers in one study (Ref. 12).

Doses higher than 1,600 mg per day (unspecified salt in 4 divided doses) in humans apparently can be considered the upper limit of usage of the drug, since above this amount generalized toxicity is observed in schizophrenic patients (Ref. 11). Below this dose, however, signs of central nervous system stimulation were apparent in the same patients.

No literature was found concerning poisoning or doses which cause death in humans.

Two uncontrolled and three controlled studies were found concerning the effectiveness of phenyltoloxamine as a sedative. Although insufficient information is available, it appears that a study by Sainz (Ref. 3) was uncontrolled. Phenyltoloxamine (dihydrogen citrate salt) was used to treat 227 cases of psychotic behavior, using oral doses of 100 to 500 mg 4 times a day. Sainz concluded that the drug has a powerful affective and behavioral effect, although it does not produce euphoria, exhilaration, mental cloudiness, or confusion. Addiction and withdrawal reactions were not noted after 6 months of continued high dosage in certain patients. For certain anxieties, the calming effect produced by the drug is, in Sainz' opinion, slightly more pronounced than that produced by phenobarbital and the meprobamates; and because of the absence of immediate or eventual reactions, much safer and preferable to either.

The other uncontrolled study was by Fleischmajer et al. (Ref. 4), who gave 500 mg per day (unspecified salt) by mouth to 50 patients with a variety of dermatoses in whom a tension factor was believed to be associated with the disorder. They found that in 39 of the patients there was excellent relaxation, lessening of inner tension, and an improve-

ment in the ability to sleep. They evaluated various dosage schedules and recommended 200 mg for nighttime sedation, with the comment that the ideal individual dose should be determined for each person.

The first controlled study, by Noell et al. (Ref. 5) was performed on over 3,000 men for the purpose of evaluating the sedative effects of more than 20 antihistamines by electroencephalographic methods and comparing these effects with those of barbiturate and nonbarbiturate hypnotics. Phenyltoloxamine (dihydrogen citrate salt) 50 mg was significantly better than placebo and ranked better than 50 mg of methapyrilene hydrochloride in the experiment on determination of onset of sleep. The dihydrogen citrate salt ranked better than diphenhydramine hydrochloride 50 mg, considered by the authors one of the three most sedating antihistamines.

The second controlled study (Ref. 12) was a comparative double-blind study with reserpine and placebo on 15 volunteers who received single oral doses of 400 mg of phenyltoloxamine (unspecified salt) 5 mg of reserpine, or placebo. Physiological measurements and a battery of psychological performance and learning tests were used to determine drug effects on behavior and function of the individuals. The results showed that 400 mg of phenyltoloxamine produced sedation and a moderate hypnotic effect, reaching a peak in 4 to 5 hours. Although latency and duration of sleep itself were not measured in this study, at the peak action of the drug there was drowsiness and a slowing of psychomotor and mental performance, followed by a state of relaxation, increased learning, and improved performance.

The third controlled study (Ref. 6) evaluated the effectiveness of phenyltoloxamine (unspecified salt, 50, 100, and 200 mg orally) as a daytime sedative, comparing it with 2 doses of phenobarbital and a placebo. One hundred thirty-one ambulatory patients, all of whom required a sedative for control of an anxiety state, were used. The workers concluded that phenyltoloxamine 3 to 4 times daily for several weeks of continuous therapy is safe. Although they did not make any comparisons with phenobarbital in their discussion, it appears that 100 mg of phenyltoloxamine was equivalent to 15 mg of phenobarbital in a "combined sedation and hypnotic effect" measure that they presented.

In summary, the Panel believes that the available data on the safety and effectiveness of phenyltoloxamine dihydrogen citrate in the dose range of 100 to 200 mg are not adequate to permit its use as an OTC nighttime sleep-aid. There is some evidence that the drug may have effectiveness as an OTC nighttime sleep-aid; for example, in one study (Ref. 5) the drug ranked better than methapyrilene hydrochloride when measuring "end of wakefulness" and better than diphenhydramine hydrochloride, on determination of "onset of sleep."

Since the ingredient is not currently marketed as an OTC sleep-aid but is currently available in an OTC combination product promoted as a calmative, it should be placed in Category III (MH) with a marketing hold during the testing provided. The Panel concludes that the available reports on the safety of phenyltoloxamine are not adequate to permit its use as an OTC nighttime sleep-aid. The Panel recommends that a minimum of five additional well-controlled studies are necessary to establish the safety and effectiveness of the ingredient as an OTC nighttime sleep-aid. At least two EEG studies and at least three clinical studies are necessary. The Panel has determined that an appropriate dosage for testing should be limited to 100 to a maximum 200 mg single dose at bedtime.

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(5) *Pyrilamine maleate.* The Panel concludes that there is insufficient information on the safety and effectiveness of pyrilamine maleate as an OTC nighttime sleep-aid and has therefore placed the ingredient in Category III. Described as an effective antihistamine with low-incidence of sedation (Ref. 1), it appears ancillary to methapyrilene as an ingredient in three currently marketed OTC products promoted for sleep. The usual single OTC dose for an adult is 25 to 50 mg. The Panel has determined that further testing in well-controlled studies is required to assure the safety and effectiveness of a suggested dosage of 25 to a maximum 50 mg single dose at bedtime. (See paragraph II D below—Data Required for OTC Nighttime Sleep-Aid Ingredient Evaluation).

Pyrilamine was discovered in France (Ref. 2) 2 years after the introduction of Antergan, the first antihistamine used clinically (Ref. 3). Pyrilamine effectively inhibits experimental production of skin wheals by histamine (Ref. 4) and can prevent the increase in capillary permeability ordinarily produced by histamine (Ref. 5). In addition to its effectiveness as an antihistamine, pyrilamine also possesses local anesthetic activity (Refs. 6 and 7) and even exerts a mild analgesic action (Ref. 8).

In doses of 25 to 50 mg, anorexia, nausea and vomiting are commonly encountered but can be minimized by the simple precaution of taking this ingredient at mealtimes. However, the Panel believes this is not possible when pyrilamine is used as an OTC nighttime sleep-aid. The Panel has located only one study pertaining to the hypnotic potential of pyrilamine used alone (Ref. 9). This study provides some evidence that pyrilamine maleate 50 mg is superior to placebo in reducing the time to "end of wakefulness" by EEG criteria but not in the subjective evaluation of "time to sleep onset." Subjects were military personnel studied under daytime nap conditions.

The Panel is aware of instances of accidental poisoning with pyrilamine. For example, two fatalities of accidental poisoning have been reported in the literature (Ref. 10). In one case a 15-month-old infant died 6 hours after ingestion of 1,500 mg of the drug, and in a second case a 23-month-old infant died 6 hours after ingestion of 10 tablets (dose unspecified). Both victims exhibited coma and/or convulsions previous to death. The Panel therefore believes that when further testing is conducted, special attention should be given to the minimum dosage level required for effectiveness.

The Panel concludes that insufficient data are available on the safety and effectiveness of pyrilamine maleate as an OTC nighttime sleep-aid and has therefore placed the ingredient in Category III. Further testing is necessary in a suggested dosage of 25 to a maximum 50 mg single dose at bedtime. The Panel recommends that a minimum of five additional well-controlled studies are necessary to establish the safety and effectiveness of the ingredient as an OTC nighttime sleep-aid. At least two EEG studies and at least three clinical studies are necessary. Should studies show safety and effectiveness, this drug could be moved from Category III to Category I.

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*Labeling*

It is the view of the Panel that the following label claims would be acceptable for OTC nighttime sleep-aid products if sufficient data were provided to substantiate their use. Labeling such as "Reduces time to fall asleep in persons with difficulty falling asleep," "Reduces number of awakenings in persons who wake frequently during the night," and "Prolongs sleep," may be valid if proven by well-controlled studies. (See paragraph II D below—Data Required for OTC Nighttime Sleep-Aid Ingredient Evaluation.)

D. DATA REQUIRED FOR OTC NIGHTTIME SLEEP-AID INGREDIENT EVALUATION

The Panel suggests the following guidelines for the evaluation of safety and effectiveness of an agent to be used as an OTC nighttime sleep-aid:

1. *Minimum requirements to determine safety and effectiveness.* The active ingredient must be safe in the doses suggested on the labeling for OTC use. Safety should be evaluated using the current requirements for preclinical testing in animals as defined in 21 CFR 312.1(a)(2)6.a. Regarding effectiveness, a number of important variables must be considered: (1) sleep latency (time required to fall asleep), (2) number of awakenings, (3) total time spent awake, (4) sleep duration, (5) sleep quality, as estimated by the sleeper, (6) sleep stages and cycles evaluated by EEG and polygraphic criteria, and (7) side effects. Typically, an OTC medication might be tested to determine whether it reduces sleep latency (or possibiy increases sleep duration) without detrimental effects on the other variables.

A target population must be identified so that wherever possible in studies of effectiveness, subjects tested are similar to those who will eventually take the drug. For OTC nighttime sleep-aids, the population would consist of individuals with symptoms of mild or occasional sleep disturbance.

It is important to provide both subjective and objective assessment of sleep. Certain important aspects, such as the subject's estimate of the quality of sleep and feeling state in the morning, can only be assessed subjectively. On the other hand, objective sleep laboratory studies have obvious advantages to assess objectively and exactly continuous measures of sleep, thus providing exact measures of sleep latency, sleep duration, number of awakenings, and other variables of interest. Other clinical aspects can also be assessed both subjectively and objectively.

Any claimed ingredient(s) or labeling claim(s) classified by the Panel as Category III should be evaluated using the concepts and methodology described below in the suggested guidelines.

2. *Sleep laboratory studies.* A small number of appropriate subjects (e.g., 6 to 12 per study) should be studied intensively in a sleep laboratory. Sleep laboratory studies should involve the use of both placebo and active medication in a properly controlled design. The exact design would depend on individual drug factors, such as time required for washout, necessity in some cases for studies of continuous administration, etc. This would allow precise determination of sleep latency, sleep duration, number and length of awakenings, and time spent in the various sleep stages. Such a study can help determine effectiveness and can also be used as a safety or toxicity study since disturbances of sleep and mood can be studied during and after drug administration. Such laboratory studies would ideally include investigation of the drug when taken on multiple consecutive nights and after discontinuation, since withdrawal effects after continuous administration can be of importance. However, since the drug is an OTC preparation to be taken as a single dose for occasional insomnia, such long-term studies are not absolutely essential, though still advisable.

3. *Clinical studies in a suitable target population.* A large number of appropriate subjects should be studied for subjective effects on sleep. Subjects should be mild insomniacs falling directly within the target population expected to take the drug. Such a study should preferably use separate large groups, perhaps 40 to 80 subjects per group, since intergroup comparisons have statistical advantages. A well planned crossover study, however, might also be acceptable. If several doses of a drug are to be studied, or if a combination of several ingredients is being studied, a larger number of groups is required. For instance, if a combination containing two ingredients (A+B) is studied, a design should include four separate groups: one taking placebo, one taking A, one taking B and one taking A+B. Subjects are to be assigned by systematized randomization with packaging and coding of the drug on an individual patient basis rather than on a treatment group basis. The Panel is concerned that the integrity of the study be maintained and that subjects are not able to determine drug from placebo, since the findings are heavily dependent on subjective parameters. The Panel suggests that each dose unit (drug or placebo) be singly identified by code and administered singly (e.g., in envelopes) in a predetermined sequence.

The variables to be investigated include the subject's estimate of quality of sleep, sleep latency, number of awakenings, sleep duration, how well he feels in the morning, and a report of any side effects.

In certain cases other designs may be reasonable; for instance, a design in which the subject indicates a preference between two treatments (drug versus placebo) may be used but would not be considered a pivotal study.

4. *Clinical studies for nighttime sleep-aids.*—a. *Objectives.* The overall objectives are: (1) to determine the effects of the drug on sleep in individuals with symptoms of mild insomnia likely to use such an OTC drug in the target population, (2) to determine the subjects' estimate of quality of sleep, an estimate of how well they feel in the morning and (3) to determine any preferences the subjects may have between 2 nights (drug versus placebo).

These studies, if results are clinically significant, will provide an extension of comparative controlled studies to confirm fully in a target population the drug's basic nighttime sleep-aid activity and to provide more specific information about symptoms and subject types in which the drug is especially effective. The studies will also establish an optimal dosage for the target population for which it is intended under conditions which more closely resemble those of actual OTC use.

b. *Sample considerations.* Subjects should be mild insomniacs falling directly within the target population expected to use the drug. Subjects with severe or chronic insomnia are not candidates for self-medication since they should be under the supervision of a physician.

A greater variety of populations differing as to age, sex, diagnostic categories, social class, treatment setting, previous treatment, etc., may be studied. Within each study, groups of subjects should be selected to be as homogeneous as possible regarding the variables above. In any case, full reporting of subjects' characteristics is necessary to allow for adequate interpretation of results. Exclusions should be stated.

Females of childbearing age may be included if results of animal reproductive and teratologic studies are satisfactory. However, the Panel believes that new drugs not intended for lifesaving use should not be used in women known

to be pregnant or who are nursing a baby.

c. *Sample size.* The studies should use separate large groups containing 40 to 80 subjects per group. In a study comparing separate groups, a minimum of two groups (drug and placebo) are necessary. A large number of groups are required if several doses of a drug are studied or if a combination of several ingredients is evaluated, since each ingredient should be compared to the combination and a placebo.

d. *Setting.* Varying environmental influences should be decreased as much as possible in each study. Different treatment environments may be used which should be similar to those likely to be found among users (consumers) of such OTC products. Since these drugs are indicated for nighttime use, their action should not persist into the daytime hours or beyond the intended period of sleep.

e. *Investigators.* The investigators should be experienced in evaluating drugs affecting the central nervous system; and in the conduct of clinical trials; they should have ready access to the target population group for whom the nighttime sleep-aid may be indicated.

f. *Design.* Of primary importance are well-controlled studies designed to confirm fully the effectiveness of the drug as a nighttime sleep-aid. Special consideration should be given to controls, duration of study, dosage, and design which do not interfere with validity (biostatistical consultation is recommended), to accommodate greater variations in settings and subjects.

g. *Duration.* The duration of studies may vary from 1 to 2 weeks. In most cases the drug will be taken as a single dose for occasional insomnia, and therefore long-term studies are not absolutely essential. However, the Panel believes that such studies are advisable.

h. *Assessment.* Activity as a nighttime sleep-aid should be determined by accepted methods. Determination of clinical effectiveness should include subjective reports from patients or subjects and EEG and inpatient studies should also include objective measures.

5. *General concepts for conducting clinical drug evaluation of OTC nighttime sleep-aids.* The Panel concurs with the current regulations for conducting clinical trials evaluating safety and efficacy as defined in 21 CFR 314.111(a)(5)(ii). The desired studies shall include a systematic assessment of possible adverse side effects as discussed above under clinical studies for nighttime sleep-aids and shall include continued surveillance for adverse side effects after marketing.

6. *Minimum data required for classification as a Category I ingredient.* In summary, the Panel believes that similar methodology should be used in the evaluation of an OTC nighttime sleep-aid as in the evaluation of a prescription hypnotic with two major exceptions:

(1) Only those who are occasionally insomnic are included.

(2) A larger patient sample than is customary in the evaluation of prescription drugs is probably necessary for a parallel design study (for example, 80 and not 40 patients per drug group may be needed), since relatively smaller clinical effects may be encountered.

E. COMBINATIONS OF ACTIVE INGREDIENTS

1. *General statements.* The Panel concurs with the 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 directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

The Panel concludes that, in general, the fewer the ingredients, the safe and more rational the therapy. The Panel believes that the interests of the consumer are best served by exposing the user of OTC drugs to the fewest ingredients possible at the lowest possible dosage regimen consistent with a satisfactory level of effectiveness.

The Panel further concludes that OTC drugs should contain only such inactive ingredients as are known to be safe and are necessary for pharmaceutical formulation.

2. *Requirement of significant contribution.* The Panel has determined that each claimed active ingredient in a combination must make a significant contribution to the claimed effect or effects.

The Panel could not establish the percent of contribution that an active ingredient must make to the effectiveness of the product for that contribution to be considered "significant." The Panel concludes that where a combination product is permitted, as discussed below, it is sufficient to demonstrate in well-controlled clinical trials that each of the ingredients makes a statistically significant contribution to the claimed effect. (See paragraph II D above—Data Required for Nighttime Sleep-Aid Ingredient Evaluation.) As long as "statistical significance" is shown in meaningful sample sizes, the Panel concludes that the contribution toward nighttime sleep-aid activity will also have been shown to be clinically "significant."

3. *Single active ingredients.* The Panel believes that the most desirable product for the consumer is one that contains the least number of ingredients. A product containing a safe and effective single ingredient is preferred to one having multiple active ingredients because of the reduced risks of toxic effects, allergic and/or idiosyncratic reactions, and possibly unrecognized and undesirable drug interaction(s). Because of these increased risks, the Panel further believes that the use of two active ingredients of the same pharmacological class in the same preparation is not rational.

This view of the Panel applies to all ingredient combinations that the Panel has reviewed; even the antihistaminic drugs cause non-dose-related adverse reactions, such as drug allergy. In other words even the presence of two antihistamines may increase the risk that a subject will have an allergic response to the OTC preparation. A person may not be allergic to one of the two active ingredients whereas he might respond with an allergic reaction to the other. Paradoxically, such hypersensitivity reactions do occur to the antihistamines, drugs which are themselves often used to treat allergic responses.

Certain problems peculiar to the formulation of combination products should be stated explicitly before dealing with specific cases. First of all, there are situations where the use of a combination is appropriate and clearly rational. Such an example is the case of the "triple sulfas" described below.

The misconception about the safety of using more than a single member of a pharmacologic class of drugs seems to be based upon a very special case. When the sulfonamides were introduced to clinical medicine, it became apparent that their low solubilities (particularly in the large doses nedeed to treat certain bacterial infections of the urinary tract) could result in precipitation of crystalline drug in the kidney. This problem was solved by using combinations of sulfonamide drugs, e.g., "triple sulfas," such that each of the three sulfonamides was present in an amount too small to crystallize out in the kidney but such that the combined three sulfonamides provided an effective therapeutic concentration. The basis for this effect is the fact that the solubility of each member of the series is independently determined. No such problem of dosage scheduling that approaches saturation leading to crystallization has been noted by the Panel in its review of the antihistamine drugs submitted.

The Panel is aware of other cases where multidrug therapy is rational. Two different antibiotics may be given together for an organism known to be sensitive to the combination. Perhaps one of the best known combinations is the use of multivitamin preparations for the treatment of nutritional deficiencies. In these last two cases, the combination is used to achieve a certain convenience where the individual active ingredients are known to be effective separately. The Panel recognizes that in vitamin and in certain antibiotic therapy, a large dose of drugs usually, but not always, carries no more risk than a smaller dose. This is an unusual situation in medicine.

If an OTC nighttime sleep-aid is indicated, it may very well be that a consumer will need one or two doses to get the intended effect. An occasional subject may need half of the suggested dose. If an analgesic is also needed, the consumer, through experience, will be able to judge wether he needs one, two, or one-half of the usually recommended OTC analgesic dose. If a consumer needs an OTC nighttime sleep-aid alone or an OTC analgesic alone, it would be an irrational act to take a combination product.

The Panel questions the advantage the combination confers. If the consumer cannot fall asleep readily, he may wish to take an OTC nighttime sleep-aid for this condition. He may also have some discomfort due to an injury, infection, burn or other ailment and may wish to take an OTC analgesic. The Panel feels that the likelihood that a combination drug will contain the optimal dose is less than if the consumer is permitted to make this decision, that is, to take individually an analgesic and/or nighttime sleep-aid.

Evidence accumulated during the last 20 years indicates at least a 10-fold difference within the population in the rate of disappearance from the body for most drugs subject to metabolism. Moreover, different kinds of drugs are eliminated at different rates by each individual.

In light of present knowledge, it is not wise to give two or more different active ingredients in fixed combinations to different individuals.

In addition, it does not make sense unless there is information that the effective dose of each active ingredient is known for the individual taking such a combination.

A very simple exercise will demonstrate the decreasing benefit to be expected when two or more active ingredients are combined in a single preparation. Suppose that 60 percent of the population requires one unit of drug A for relief of pain. Now, combine A with ingredient B, a drug that promotes sleep. Assume that, by good fortune, a dose of B is found that will have a favorable effect on 60 percent of the population. The chances that the 60 percent who need one unit of A will also need one unit of B is 0.60x0.60, or 36 percent. Thus, by combining we have reduced the chance of a successful outcome for both indications from these preparations. (The number of people who need half of A and half of B or two of A and two of B are vanishingly small and may be ignored for present purposes.) One could add yet a third active ingredient (certainly not unheard of) and find that the appropriate population for this preparation would be 0.60 x 0.60 x 0.60, or 22 percent of consumers.

Thus the Panel believes, that even if the addition of another active ingredient represents addition of a potential benefit to an existing product, the changes that the consumer will benefit from a fixed combination is in fact less likely than if that individual has the option to use active ingredients separately.

The Panel notes that individuals metabolize different active ingredients at vastly different rates and may eliminate them at different rates.

These biochemical differences are the basis for different dosage requirements on the part of individual human subjects. Ordinarily, in a relatively small group of persons there may be as much as a 10-fold difference in the rate of metabolism of a drug. The effect of these differences becomes apparent in the case of drugs used chronically. For OTC drugs used only occasionally and for nonfatal illnesses, it is not necessary to ensure that the dosage provided will be effective for 90 or 100 percent of the population. A 2- to 4-fold variation in the dose needed may be expected to achieve a desired effect in a significant proportion of the population. It has been pointed out above by simple calculations, using the probability of independent events, that combinations may reduce the likelihood of achieving the most effective dosage regimen because of differences between individuals with respect to drug metabolism. The implications of this knowledge for dosage requirements, in the Panel's view, casts some doubt upon the combination of nighttime sleep-aids and analgesics. These remarks are intended to apply to the kinds of active ingredients with which the Panel has been concerned.

In spite of the considerations above, the Panel recognizes the argument that there may be convenience in putting more than one active ingredient into the same product. The Panel concludes that if a combination contains an analgesic and a nighttime sleep-aid, both of which are safe and effective when used alone, it is convenient to combine the ingredients in a combination for the treatment of concurrent symptoms. The Panel would recognize the combination as safe and effective (effective as both a nighttime sleep-aid and as an analgesic in a significant proportion of the population having both sleeplessness and pain at the same time). The Panel concludes that permission to market such a combination should be granted. However in the opinion of this Panel, it will be necessary to demonstrate that there exists a well-defined target population that requires both a nighttime sleep-aid and an analgesic. Several studies are necessary using a factorial design demonstrating that the combination is safe and effective for a significant proportion of the target population requiring relief from both symptoms of pain and sleeplessness.

The labeling of a combination product of the type described above should reflect its limited applicability to persons with both symptoms, pain and sleeplessness, who respond favorably to the unit dose of each active ingredient in the combination The labeling should indicate that only that portion of the target population having both indications at the same time may be expected to derive effective and safe responses to the fixed combination.

It is an established medical principle to give only those medications, preferably as single entities, necessary for the safe and effective treatment of the patient. This principle applies equally to self-medication. To add needlessly to the patient's medication increases the risk of adverse reactions. Therefore, only single ingredients of each pharmacologic class should be permitted in Category I combinations. Combinations containing more than one active nighttime sleep-aid ingredient of the same pharmacological class are classified as Category II products.

4. *Active ingredients not reviewed by the Panel.* Each claimed active ingredient must be an ingredient that has been reviewed by the Panel. If a product contains an active ingredient that has not been reviewed by the Panel and consequently is not found in this document, such ingredient is automatically classified as a Category II ingredient; i.e., it is not generally recognized as safe and/or effective. Appropriate animal and human testing and prior approval by the Food and Drug Administration are required before a product containing such an ingredient may be marketed.

5. *Review of submitted combination products.* The Panel considered only those combination products submitted pursuant to the notice published in the FEDERAL REGISTER of August 22, 1972 (37 FR 16885) and included above in paragraph II A. The Panel recognizes that other combinaton products may be in the market place, but it has either no knowledge of such products or insufficient data with respect to such products to make a reasonable judgment of safety and/or effectiveness.

Accordingly, the Panel recommends that any new combination, or any presently marketed combination not submitted to this Panel, be evaluated through the new drug procedures or be the subject of an appropriate petition to the Commissioner to review or amend the OTC nighttime sleep-aid monograph.

6. *Combinations containing irrational ingredients.* The Panel has reviewed those nighttime sleep-aid ingredients which are in combination with such nonnighttime sleep-aid ingredients as vitamins and passion flower extract. The Panel considers such combination to be irrational.

For example, generally, a healthy individual ingesting a well-balanced diet will receive adequate daily vitamin intake. The Panel defers to the OTC Vitamin, Mineral and Hematinic Panel on the safety, effectiveness and labeled claims for vitamins. However, the Panel is of the opinion that most clinicians agree that the therapeutic use of vitamins should be restricted to the treatment of unequivocal deficiency states or as dietary supplements in certain clinical situations, such as (1) inadequate intake due to poor diet, (2) malabsorption, (3) pregnancy, or (4) hypermetabolic states producing increased tissue requirements.

The proper functioning of all cells requires an adequate intake of all vitamins (water-soluble and fat-soluble). It is misleading to assume or propose that individuals consuming certain OTC sleep-aids, tranquilizers and sedatives have selected deficiencies of just those water-soluble vitamins discussed in this document. Vitamin deficiencies are generally manifold and not restricted to one or two vitamins. If treatment of vitamin deficiencies is indicated, high doses are used and ordinarily several vitamins are given, particularly in the case of water-soluble vitamins. Also, there is virtually nothing in the current medical or pharmaceutical literature to support the inclusion of selected water-soluble vitamins in the OTC nighttime sleep-aids, daytime sedatives, or stimulants. The water-soluble vitamins discussed in this

document appear to be of no use in conditions unassociated with vitamin deficiency or impending deficiency. In addition to the irrationality, there is a danger in the possibility that administration of one or two vitamins in small amounts may delay proper diagnosis and treatment in occasional cases of true deficiency. The vague suggestion in the labeling of such products is that "nerves" may be the reason for wakefulness, anxiety or agitation and that B-vitamins are good for the nerves. This claim whether explicit or implicit in the labeling is not supported by objective and conclusive clinical data.

7. *Criteria for determining Category I combinations.* Although the Panel has not placed any products containing combinations of active ingredients in Category I, it feels that appropriate guidelines are necessary. Accordingly, to qualify as a Category I combination, i.e., one that is generally recognized as safe and effective, each of the following conditions must be met:

a. The combination should include only one Category I active nighttime sleep-aid ingredient from a given pharmacological class when such ingredient(s) is identified.

b. Each ingredient in the subject combination will have to be present within the dosage range for a Category I active nighttime sleep-aid ingredient when each such ingredient is identified.

8. *Criteria for Category II combination products.* A combination is classified by the Panel as a Category II product, i.e., one that is not generally recognized as safe and/or not generally recognized as effective, if any of the following apply:

a. The combination contains two or more antihistamines as nighttime sleep-aid ingredients.

b. The combination contains any ingredient that is listed elsewhere in this document as a Category II ingredient.

c. The combination contains any active nighttime sleep-aid ingredient that has not been reviewed by the Panel and accordingly not listed in this document.

d. The combination contains a nighttime sleep-aid ingredient combined with a nonnighttime sleep-aid ingredient which the Panel has found to be an irrational ingredient.

e. The following combinations have been classified by the Panel as Category II:

(1) *Combinations containing two or more antihistamines.* The Panel concludes that there is no rationale for combining two or more drugs of the same pharmacologic class to achieve a desired effect. There are no data to support claims of safety and effectiveness of such combinations.

(2) *Combinations containing bromides (ammonium, potassium and sodium).* The Panel concludes that combinations containing ammonium bromide, potassium bromide or sodium bromide are not safe for OTC use.

(3) *Combinations containing scopolamine compounds (scopolamine aminoxide hydrobromide and scopolamine hydrobromide).* The Panel concludes that combinations containing scopolamine aminoxide hydrobromide or scopolamine hydrobromide are not safe at dosage levels possibly effective at OTC nighttime sleep-aids.

(4) *Combinations containing passion flower.* The Panel concludes that there is no rationale for adding passion flower to a nighttime sleep-aid. The relationship between the ingredient and sedation has not been demonstrated.

(5) *Combinations containing vitamins [all vitamins, including thiamin (vitamin $B_1$), niacin (nicotinic acid), and niacinamide].* The Panel concludes that there is no rationale for adding vitamins to a nighttime sleep-aid. The relationship between vitamins and sedation has not been demonstrated.

9. *Criteria for Category III combination products.* A combination is classified as a Category III combination if the nighttime sleep-aid active ingredient is classified as Category III elsewhere in the document.

The following combinations have been classified by the Panel as Category III:

a. *Combinations containing methapyrilene and certain analgesics (acetaminophen, aspirin, and salicylamide).* These combinations are placed in Category III for two reasons, (1) the sleep-aid components have been categorized as Category III by the Panel; and (2) the Panel has insufficient information to identify a meaningful target population. Additional studies are required to show that there is a target population requiring ingredients for both pain and sleep. Experimental design for such studies should include double-blind investigations using a factorial design testing the combination against each ingredient and placebo. If evidence is not forthcoming within 3 years that each ingredient (e.g., the claimed nighttime sleep-aid and the analgesic) makes a meaningful contribution to the claimed effect, these products should be withdrawn from the market.

The Panel concludes that combinations containing a nighttime sleep-aid and an analgesic are not rational therapy for patients suffering from sleeplessness or pain alone.

In a combination drug containing a nighttime sleep-aid ingredient and one or more analgesic compounds such as acetaminophen, aspirin or salicylamide, these latter ingredients are considered only as analgesics. If the analgesic component is judged effective by the OTC Panel on Internal Analgesics, if the sedative component can be proved to be an effective nighttime sleep-aid, and if well-controlled studies can identify a meaningful target population for use of such a combination, then the combination may prove to be rational for concurrent use, i.e., for sleeplessness when accompanied by pain. For example, in a currently marketed sleep-aid combination product containing methapyrilene and analgesics reviewed by the Panel, the manufacturer recommends "For best results, adults take two tablets at bedtime to help relieve pain and aid sleep." Thus, according to the manufacturer's claim, this particular combination is recommended for nighttime use in patients suffering from a combination of pain and insomnia or from "insomnia expectation." The analgesic combination, when taken as recommended, namely, two tablets, seems to be a fairly appropriate mild analgesic, although the final decision regarding this effect is deferred to the OTC Internal Analgesic Panel. The sleep-inducing properties of methapyrilene 50 mg (2 tablets) have been discussed earlier. The Panel concluded that at least some evidence exists that methapyrilene may induce sleep slightly faster than placebo and therefore placed methapyrilene in Category III.

Whether the combination of an analgesic and a nighttime sleep-aid enhances the effectiveness of either type of agent cannot be answered from the data reviewed. Only a factorial design (Ref. 1) comparing the combination with a placebo would provide the answer. One may well postulate that once pain is relieved by the analgesic component, the patient will sleep even without a nighttime sleep-aid. On the other hand, the nighttime sleep-aid may indeed provide additional benefits. The studies submitted do not provide an answer to these uncertainties.

In any studies designed to evaluate such a combination, subjects selected should be individuals with pain as well as sleep problems. A more elaborate design could include a group of subjects with both pain and sleep problems, a group of subjects with only sleep problems, and a group of subjects with only pain, but the first factorial design is considered sufficient.

The data presented to the Panel do not establish whether patients use the combination primarily for pain or primarily for sleep induction. The combination seems to be proposed primarily as a pain reliever, implying that if one does not have pain, one will sleep well. The combination is not suggested for the general insomniac.

The manufacturer produced seven well-designed, well-controlled studies in support of his claim: Four of these studies were "analgesic-sedative studies" conducted in patients suffering primarily from pain, possibly associated with secondary sleep disturbances (Refs. 2 through 5); one was a study of chronic insomniacs in an outpatient population (Ref. 6); one was a study conducted in a nursing home (Ref. 7); and one was an experimental study conducted in normal subjects who were loaded with water to produce wakefulness (Ref. 8).

All seven studies were generally well done, some involving an acute type of experiment, with each patient receiving one medication; a few studies involved giving medication to geriatric patients and other outpatients over a longer period of time. The most clear-cut and best designed experiments are some of the acute experiments (Ref. 3). They indicate clearly that the combination is more effective than placebo in inducing sleep, creating a better quality of sleep, and reducing pain. But even here, some authors have used letters (i.e., A, B) and

(9) Gross, P., R. T. P. deTreville and M. N. Haller, "Asbestos Versus Nonasbestos Fibers; Ultramicroscopic Criteria," *Archives of Environmental Health*, 20:571–78, 1970.

(10) Rohl, A. N. and A. M. Langer, "Identification and Quantitation of Asbestos in Talc," *Environmental Health Perspectives*, 9:95–109, 1974.

## III. Daytime Sedatives

### A. General discussion

1. *Definition of terms.* As indicated in the beginning of this document, the Panel is unable to define the term "tranquilizer" in relation to drugs for OTC use. The Panel concludes that "tranquilizer" drugs are more properly identified with medically prescribed psychotropic drugs (such as chlordiazepoxide and diazepam) which are available only by prescription and are "controlled substances" under the Federal Controlled Substances Act. It is the view of the Panel that the term "tranquilizer" in relation to OTC products is misleading to the consumer for it promises a qualitatively different effect from that which an OTC drug can provide. Therefore, the Panel has adopted and uses the term "OTC daytime sedative" to describe an OTC drug claiming daytime mood modifying indications such as "for the relief of occasional simple nervous tension."

2. *Benefits and risks.* The Panel is charged with examining the broad area of benefits and risks of OTC medications. The risks of OTC daytime sedatives are discussed in detail below when specific classes of ingredients are considered. The Panel will consider first the question of benefit. The possible determination of whether a benefit is produced by a drug must precede testing for "effectiveness." The Panel recognizes that even the most convincing demonstration of effectiveness in producing a change is worthless if the change is detrimental or is of no benefit to the consumer. This consideration is always present, though in some instances the benefit obtained is relatively obvious. The Panel agrees that being relieved of a headache is a benefit, and this Panel has specifically agreed that being relieved of difficulty in falling asleep can be a benefit. However, the Panel is not convinced that there is a benefit inherent in the changes claimed to be produced by OTC daytime sedatives.

The labels suggest these substances are useful for "occasional simple nervous tension," "nervous irritability," "simple nervousness due to common everyday overwork and fatigue." The claims further suggest use of these products as "calmatives," that provide "a relaxed feeling" and that "gently soothe away the tension." The Panel questions whether these claims refer to any definable illness, syndrome or condition requiring medication. And the Panel has grave doubts as to whether the relief of such a "state" constitutes a benefit to the user.

In a situation characterized by a nonexistent or almost nonexistent benefit, even a small or moderate risk clearly produces an unacceptably low benefit-to-risk ratio.

The major class of drugs reviewed for use as OTC daytime sedatives is the antihistamine group. In its discussion of OTC nighttime sleep-aids, the Panel has concluded that some antihistamines are probably useful, at appropriate doses, in producing drowsiness and sleep. This same effect, however, constitutes a risk in daytime use. The Panel concludes the sedative effect of OTC nighttime sleep-aids can be hazardous in ambulatory patients whose daytime activities require mental alertness and coordination. This may occur due to the residual effects of antihistamines persisting into the waking state after treatment of sleep difficulties. This implies that a consumer taking the same drug during the waking hours would be at greater risk from drowsiness, reduced reflex response and the like because his body would not have had time to eliminate a large proportion of the drug. Thus, drowsiness and reduced ability to respond must be considered a risk in daytime use.

In the case of antihistamines the Panel doubts that there is any anti-anxiety effect separable from the production of drowsiness. The Panel believes that such anti-anxiety psychotropic activity, if it exists, most likely would be masked by the drowsiness effect.

3. *Suitable target population.* Based on the available scientific data submitted for currently marketed products and a review of the literature, the Panel at this time is unable to determine any demonstrable indications for which available OTC daytime sedatives are useful.

An appropriate and properly defined condition, and clearer than presently used claims for a suitable target population requiring such medication, must be established through the testing guidelines set forth later in this document before meaningful studies of effectiveness can be undertaken. (See paragraph III D below—Data Required for OTC Daytime Sedative Ingredient Evaluation.)

The Panel is aware of the argument that there is a population which has anxiety symptoms for a short period of time, e.g., illness in the family, change in circumstances, loss of job, in which there would be some possible benefit from use of an OTC product while the person is adjusting to and overcoming this altered mood. One may well assume that such short term mild anxiety symptoms will clear up without treatment and/or are susceptible to the placebo effect. It is contended by others that the OTC product would either reduce the duration of symptoms or improve the person's symptoms during the period of stress. The Panel entirely disagrees with this view and believes that studies are needed to identify and define clearly such a target population for whom these drugs are intended to provide relief.

4. *Measurements of tension.* The Panel notes that whereas with the present state of medical knowledge normal tension or changes in mood cannot be properly defined or measured quantitatively in a target population for OTC use, other forms of tension can be measured. For example, depression, anxiety, somatic complaints attributed to emotional factors and psychoneurotic states can be measured and it is possible to note modifications or decreases in psychic tension with the use of tranquilizers.

There should be some mechanism to determine the level of tension for these anxiety-like symptoms which at this time the Panel believes to be so subtle, transient, and subjective, that they are difficult to measure. As studies are confined to more and more benign conditions, the likelihood of discriminating between drug and placebo effect becomes smaller and smaller, and questions of practical significance become more and more central. The Panel concludes that it is necessary to prove the safety and effectiveness of the ingredients classified as Category III for the indication "occasional simple nervous tension."

5. *Duration of treatment.* Another problem arises when the Panel attempts to determine the appropriate duration for use of an OTC preparation. It is the view of the Panel that if a suitable indication is identified, then an OTC daytime sedative should not be used beyond 2 weeks for a single episode. If an individual has "occasional simple nervous tension" every day for longer than 2 weeks, then he is likely to be taking an OTC daytime sedative for a condition which requires medical intervention. The Panel is concerned that such self-treatment with an OTC daytime sedative may encourage an individual to use these products at higher doses than recommended, or for longer than a 2-week period, and would increase the likelihood of undesirable side effects developing. In addition, such an individual would probably not seek appropriate medical assistance thereby risking more severe psychiatric symptoms.

6. *Summary of findings.* The Panel concludes that an OTC daytime sedative should not induce excessive drowsiness, reduce alertness, or produce physiologic dependency, tolerance with continued use, or significant toxicity in accidental overdose. In addition, an OTC daytime sedative should exhibit significant effectiveness in relieving anxiety-like symptoms of occasional single nervous tension as demonstrated in well-controlled, double-blind clinical studies in comparison with placebo and positive controls (Ref. 1).

The Panel finds no evidence of benefit from OTC daytime sedatives. The Panel questions whether an appropriate target population exists; and the Panel believes that any possible "anti-anxiety" benefit is inextricable from the "drowsiness" risk. For these reasons the Panel concludes that the benefit-to-risk ratio for this group of agents is unacceptably low.

REFERENCE

(1) Rickels, K. and P. T. Hesbacher, "Over-the-Counter Daytime Sedatives: A Controlled Study," *Journal of the American Medical Association*, 223:29–33, 1973.

7. *Minority statement of the Panel.* Because the Panel was unable to totally agree on all aspects of this document, the following minority statement is made:

not randomly selected numbers for patient assignment, thus allowing for possible breaking of the double-blind by associating improvement with a given letter. The problem with all of these investigations is that they were designed to show effectiveness of the combination. They were not designed to find out whether both the analgesic and antihistamine medications are needed or whether all patients with pain and pain-related insomnia, or even only expected insomnia, would have been improved just as well with only the analgesic medication.

These seven well-designed studies do not define the relative effectiveness of the hypnotic and analgesic ingredients in the combination.

In an analgesic nighttime sleep-aid combination such as that discussed above, the Panel comments as follows:

The general regulations for the OTC review require this Panel to address drug active ingredients and claims, rather than finished total products. In this case, the Panel is required to determine which ingredient in the combination product has activity as a nighttime sleep-aid and which ingredients have activity as analgesics. The Panel cannot, as was suggested in one submission, set aside this requirement and merely determine that the whole product is safe and effective.

The Panel has concluded elsewhere in this document that there are inadequate data on the effectiveness of methapyrilene at the dosage in one of the combinations submitted for review to the Panel to permit its classification as generally recognized as safe and effective (Category I). Accordingly, the combination is placed in Category III with 3 years allowed for testing. A claim for this combination is that it is a safe and effective aid to sleep that is disturbed by pain. The Panel regards such claims primarily as analgesic claims, rather than nighttime sleep-aid claims.

Pain may indeed prevent sleep, as might acid indigestion, coughing or sunburn. If the Panel were to follow the rationale that pain discomfort prevents sleep, and that something which affords relief from pain discomfort can therefore be considered a nighttime sleep-aid, it would be necessary to permit the use of a similar nighttime sleep-aid claim for any ingredient used to treat any condition that might interfere with sleep. Such ingredients might be antacids, cough remedies, or sunburn lotions. It is obvious that such drugs are not intended to induce sleep per se. If evidence is not forthcoming to support the presence of Category III antihistamines such as methapyrilene or pyrilamine as active OTC nighttime sleep-aid ingredients in combination with analgesics, nighttime sleep-aid labeling claims made on the basis of analgesics alone would be misleading.

The Panel is aware that there may well be a significant number of people suffering from both pain and sleeplessness caused by factors other than pain. An analgesic nighttime sleep-aid combination could be rational for such a group, in the Panel's opinion. Its target population, however, would include only those individuals suffering from both symptoms simultaneously. Labeling for such a combination would have to state clearly that it is for use only when both symptoms occur together, not only that one or the other is anticipated.

For combinations containing both antihistamines and analgesics, additional studies are required to show that there is a target population requiring ingredients concurrently for both pain and sleep. Experimental design for such studies should include double-blind investigations using a factorial design testing the combination against each ingredient and placebo. If evidence is not forthcoming within 3 years that each ingredient (e.g., the sleep-aid and the analgesic) makes a meaningful contribution to the desired effect, the product should be withdrawn.

10. *Inactive ingredients.* The Panel concludes that OTC drugs should contain only such inactive ingredients as are necessary for pharmaceutical formulation and are known to be safe (e.g., talc is considered unsafe).

REFERENCES

(1) Rickels, K., "Clinical Evaluation of OTC Agents," *Journal of Clinical Pharmacology,* 14:153–154, 1974.

(2) Emich, J. P., Jr., "A Study of Sleep Induction by a Mild Non-Prescription combination Drug," Draft of unpublished paper in OTC Volume 050043.

(3) Smith, G. M., C. G. Coletta, S. McBride and B. McPeek, "Use of Subjective Responses to Evaluate Efficacy of Mild Analgesic-Sedative Combinations" *Clinical Pharmacology and Therapeutics,* 15:118–129, 1973.

(4) Kantor, T. G., "Sleep Induction Study W–1752 III," Draft of unpublished paper in OTC Volume 050043.

(5) Sunshine, A., "A Comparative Study of Excedrin P.M. and Placebo," *Journal of Clinical Pharmacology,* 14:166–171, 1974.

(6) Wolff, B. B., "Evaluation of Hypnotics in Outpatients with Insomnia Using a Questionnaire and a Self-Rating Technique," *Clinical Pharmacology and Therapeutics,* 15: 130–140, 1974.

(7) Stern, F. H., "Sleep-Inducing Properties of a Nonbarbiturate Analgesic/Sedative Preparation in Elderly Patients," *Clinical Medicine,* 31–33, 1972.

(8) Condouris, George A., "Experimental Sleep Prolongation Studies" is included in OTC Volume 050024.

F. INACTIVE INGREDIENTS

The Panel is aware that "active ingredients" are defined as those which contribute to the claimed effect of a drug. All other ingredients in the drug are regarded as "inactive ingredients" even though they may have pharmacologic activity at higher concentrations or in other formulations.

With respect to the safety of "inactive ingredients" in OTC nighttime sleep-aids, daytime sedatives and stimulants, the Panel has been concerned about flavoring agents, coloring agents and particularly talc. Because of the safety considerations, the Panel has prepared the following statement on talc:

*Talc*

The presence of talc in foods, drugs, water and beverages has been noted (Refs. 1, 2 and 3). Inhaled talc containing asbestos is known to be hazardous, and even carcinogenic. The effect of ingested talc in man is not known, but animal experiments indicate that talc and asbestos, commonly a contaminant of talc, do cross the intestinal epithelium and become widely disseminated (Refs. 4 and 5). In addition, a high incidence of stomach cancer has been noted in Japanese men who eat talc-coated rice (Ref. 1). Langer has stated that talc is contaminated often with asbestos and that this contamination is difficult to detect except by x-ray diffraction and electron microscopy (Ref. 6). This is an important consideration because the carcinogenic potential of asbestos is well established.

One property of asbestos used to differentiate it from other fibrous minerals is the step-like ends of the fibers as seen with the electron microscope (Refs. 7 and 8). This is evident at magnifications of 20,000 to 25,000 and helps to detect asbestos fibers in the presence of other silicates such as talc or glass which do not share this feature (Refs. 9 and 10). The detection of the different forms of asbestos requires a combination of chemical treatment and x-ray diffraction analysis as well as electron microscopy. A complicating factor is the particle size of the fiber which is a function of the method of preparation for industrial use (Ref. 7).

It is strongly urged by this Panel that talc containing asbestos, a nonessential ingredient, not be permitted to be formulated in OTC products that are meant to be ingested. Substitute materials are available. The Panel notes that talc is described in the United States Pharmacopeia XIX as a pharmaceutic aid but is designated for external use only. The Panel notes also the statement by the Commissioner published in the FEDERAL REGISTER of March 14, 1975 (40 FR 11865) in which the problem of the nonessential and avoidable use of talc is discussed. The Panel concludes that due to the lack of safety, talc containing asbestos should not be permitted in OTC nighttime sleep-aids, daytime sedatives and stimulants.

REFERENCES

(1) Merliss, R. R., "Talc-Treated Rice and Japanese Stomach Cancer," Science, 173:1141–42, 1971.

(2) Nicholson, W. J., C. J. Maggiore and I. J. Selikoff, "Asbestos Contamination of Parenteral Drugs," *Science,* 177:171–73, 1972.

(3) Cook, P. M., G. E. Glass and J. H. Tucker, "Asbestiform Amphibole Minerals: Detection and Measurement of High Concentrations in Municipal Water Supplies," *Science,* 185:853–4, 1974.

(4) Pontefract, R. D. and H. M. Cunningham, "Penetration of Asbestos Through the Digestive Tract of Rats," *Nature,* 243:352–53, 1973.

(5) Selikoff, I. J., "Personal Communication," 1973.

(6) Langer, A. M., "Personal Communication," 1975.

(7) Rubin, Ivan B. and C. J. Maggiore, "Elemental Analysis of Asbestos Fibers by Means of Electron Probe Techniques," *Environmental Health Perspectives,* 9:81–94, 1974.

(8) Langer, A. M., et al., "Electron Microscope Investigation of Asbestos Fibers," *Environmental Health Perspectives,* 9:81–94, 1974.

For the group of drugs classed as OTC daytime sedatives the minority has found no clear evidence of effectiveness, and no sharply defined indications. If the antihistamines are used in doses that have sedative effects these will be due to a general, nonspecific central nervous system depression.

If effective, in larger doses, the central depression carefully outlined for the use of these drugs as OTC nighttime sleep-aids would be dangerous to the user and/or others in the view of the minority. Such effects have been observed as side effects in the use of antihistamines for treatment of hypersensitivity, motion sickness and other indications. Effects on driving a motor car or operating other machinery are difficult to evaluate. Sensitive techniques for such measurements are still in the process of development. The Panel's discussion holds out little hope of proving effectiveness and describes several kinds of clinical trials of more or less difficulty. Such trials would, if properly conducted, take considerable time, probably 4 to 6 years to prove effectiveness and to deal with the difficult evaluation of safety.

We believe this interval would constitute an extraordinary time to market a group of drugs not deemed effective by the minority at present doses and most probably unsafe at higher doses.

As evidence for the possible adverse effects of effective doses the minority cites the discussion (elsewhere in this document) of the warnings about antihistamines used as nighttime sleep-aids.

In accordance with these comments in the introductory section above for OTC daytime sedatives, the minority believes that the OTC daytime sedatives should be classified as Category II.

B. SAFETY AND EFFECTIVENESS

The Panel finds that currently marketed products which have been classified as OTC daytime sedatives generally contain antihistamines, scopolamines or bromides either singly or in combinations. Scopolamines and bromides have been found by the Panel to be unsafe for OTC use and will be further discussed below. Antihistamines, as stated previously in the discussion pertaining to OTC nighttime sleep-aids, may, in addition to their antihistaminic action, induce drowsiness when used in the treatment of allergies. (See paragraph II C 3.a. above—Antihistamines.)

Furthermore, with respect to the profile of pharmacological activities of the antihistamines, the Panel finds that there is little or no evidence that such drugs poses anti-anxiety psychotropic properties comparable to those demonstrated in clinical studies with the prescription tranquilizers. In the Panel's view, at best, some antihistamines may produce a very small incidence of low intensity sedative activity which would be difficult to demonstrate in a signficant portion of the population. Any anti-anxiety psychotropic activity, if it exists, most likely would be related to the "drowsiness" effect of the antihistamines.

Therefore, the Panel is concerned with a possible danger in "treating" simple and transient variations in normal mood and behavior with OTC products containing antihistamines or any similar sedating agent. The Panel believes that such drugs affecting mind and mood have much broader implications than other OTC classes of drugs (e.g., antacids, laxatives) in that alterations in an individual's mood indirectly affects other individuals. There is also possible danger that because of the excessive sedation, individuals with normal anxiety-like symptoms will involuntarily and unwittingly suffer reduced alertness, ability to concentrate and motor coordination. It is the view of the Panel that such use will restrict the individual's ability to cope with his environment. In the case of antihistamines, depressant effects appear at low concentrations and excitatory effects at high concentrations (Ref. 1); however, this varies from person to person. In some cases the excitatory effect is dominant even at low concentrations, and in other cases antihistamines produce depression throughout the normal dosage range so that therapeutic effects lack predictability.

In the general population, many people experience tension and most people have learned how to deal with it. Where tension becomes disabling, some individuals need medical assistance (e.g., counseling) and/or psychotropic medication. In such cases, effective psychotropic drugs do exist but are available only on prescription. In the review of the ingredients submitted and identified in paragraph I A 2 of this document, the Panel concludes that it is highly unlikely that such ingredients could be shown to be effective because normal tension or anxiety is difficult to measure in a target population by current medical standards.

A suggestion was made in one submission (Ref. 2) to replace alcohol use (or abuse) with OTC daytime sedatives when individuals, emotionally upset or unable to cope with particular life stresses, would normally turn to alcohol. The Panel is aware that there is massive alcohol abuse in the U.S. and that there are also thousands of people who misuse and abuse drugs in this country.

Since the primary function of OTC products is to relieve symptoms of self-limiting diseases not requiring medical intervention, the Panel has concluded that OTC daytime sedative self-medication is not safe and not effective in the treatment of serious emotional and behavioral problems, including chronic alcohol and/or drug abuse. A substitution of OTC daytime sedatives for alcohol will certainly not exert any constructive effects on the individual's basic psychological or environmental problems. Where individual subjects are using alcohol to resolve serious personal life stress problems, they most likely would require medical and often psychiatric intervention. Use of an OTC daytime sedative as a substitute for alcohol in relieving life stress is particularly contraindicated since it delays proper medical treatment.

The Panel also takes note of the fact that there is a very high frequency of cases of poisoning involving simultaneous use of sedative drugs and alcohol; the additive effects of these agents can lead to serious toxicity. The Panel is not aware of any data to support the contention that nonuse of daytime sedatives marketed for "occasional simple nervous tension," or the like, leads to abuse of alcohol or alcoholism. The epidemiology of alcohol abuse is an extremely complex subject that allows very few "causative" statements to be made. It is conceivable that there may be situations where drugs should be substituted for alcohol abuse but that is more properly the province of the physician with a great deal of experience in dealing with alcohol abuse and certainly is far beyond the scope of this Panel's inquiry.

The Panel concludes, based upon the current available data and the lack of well-defined indications for safe OTC use, that if there is to be pharmacological intervention in cases of anxiety-like symptomatology, the drugs of choice are tranquilizers available by prescription. The Panel notes that these drugs have been extensively studied and evaluated as psychotropic drugs. The Panel recognizes that methapyrilene, pyrilamine and phenyltoloxamine have been marketed for OTC daytime sedative activity. The Panel is unaware of meaningful data which demonstrate that these ingredients have psychotropic activity. Therefore, the Panel has placed methapyrilene, pyrilamine and phenyltoloxamine in Category III since available data are inadequate to show that they are safe and effective as daytime sedatives. However, the Panel emphasizes that the reason for Category III includes the Panel's determination of a low benefit-to-risk ratio and lack of an appropriate target population—not merely insufficient proof of effectiveness.

The Panel has reviewed the available published and unpublished material relating to the effectiveness of products marketed as OTC daytime sedatives. Only one controlled clinical trial evaluating the role of OTC daytime sedatives in mild to moderately anxious patients exists in the literature (Ref. 3). In this study, a claimed OTC daytime sedative containing methapyrilene, pyrilamine maleate and scopolamine is compared with aspirin, a tranquilizer and placebo in a 2-week clinical trial. The results may be summarized as indicating chlordiazepoxide to produce significantly more improvement than the other three agents which did not differ significantly from each other. In fact the OTC product was no different from placebo in effectiveness.

Besides the published study mentioned above, there are only two unpublished reports in the submissions (Refs. 4 and 5).

The first unpublished report (Ref. 4) does not provide enough details to evaluate it fully. This study uses only 25 subjects, and a design which identifies drug and placebo simply as A and B, permitting users to determine which drug they are ingesting, thus destroying the

double-blind design. The study suggests mild sedative activity of the daytime drug, but it is not possible for the Panel to draw conclusions which support the effectiveness of the drug reviewed.

The statistical results in the second unpublished report (Ref. 5) at first sight are more impressive, since the significance obtained is acceptable for clinical studies. However, the fact that patients with headaches had to be omitted for such significance to occur is unfortunate. It is well known that tension often has headache as one of its major symptoms (60 percent of the patients in this study had headache), and breaking any link in the tension-headache-tension cycle by drug treatment is usually sufficient to allay both the tension and the pain. The Panel suggests that one of the major areas for testing is whether an OTC daytime sedative can relieve the tension-headache-tension cycle itself or must be in combination with an analgesic.

One other problem concerns the choice of subjects. These were patients who were seen for "other complaints which did not interfere with the evaluation of the sedative." It was not clear how the inestigators were sure of that fact. Almost any complaint considered serious enough for the patient to consult his physician could be associated with some degree of stress, which might conceivably interfere with a tension-sedative treatment program.

The possibility mentioned by the authors that some patients took aspirin during the study period is unfortunate because aspirin could significantly alter the tension state by reducing a headache or other nagging body pains which contributed to the tension state. Since the authors did not indicate the number of patients who took aspirin, it is difficult to evaluate its effect on the results obtained.

Finally, in the first part of the study, in a sample group of 87 patients, drug and placebo responses were practically identical. Drug-placebo differences were only obtained in the crossover portion of the study and no differences were observed comparing the OTC sedative (N=40 patients) and placebo (N=47 patients) when given first (Ref. 6).

This report is the only one available to date which may possibly be considered as providing some support for the effectiveness of an OTC daytime sedative. However, the separation between tense individuals who have and who do not have headache, both for the purpose of producing statistical significance in the study and for identifying potential users of the OTC drug in practice, does not seem to be a realistic approach in light of the frequent occurrence of headaches in tense individuals. In addition, the OTC drug was often used only once daily, and without having data as to the time of day the drug was taken. One cannot exclude the possibility that the OTC drug was primarily used in the evening, as a mild sleep inducer and not as a daytime sedative, since it might tend to slant the results toward greater effectiveness.

In summary, the Panel is aware of only one published controlled study (Ref. 3). This study established clearly the methodology for clinical studies of OTC daytime sedatives and the ineffectiveness of the OTC sedative combination in relieving mild anxiety tension. The only claims of effectiveness of OTC daytime sedatives have been offered by two submissions to the Panel (Refs. 5 through 8). Of the data submitted, only one study (Ref. 5) presents data on the effectiveness of OTC daytime sedatives and that study has deficiencies discussed earlier in this document.

After reviewing all available data, the Panel therefore concludes that there is lack of sufficient evidence presently available to support the use of OTC daytime sedatives. Only after an indication can be identified, the sedating effects of antihistamines are resolved and a number of well-designed double-blind clinical studies demonstrate significant drug-placebo differences, could such drugs be recommended for OTC daytime sedative use. The Panel doubts however that the claimed effects are more than placebo effects.

*Labeling*

The Panel has found difficulty in establishing labeling for OTC daytime sedatives. Since currently marketed products contain antihistamines, the Panel recommends that such products contain the following warning: *"Caution:* This product contains an antihistamine drug and may cause drowsiness. Avoid driving a motor vehicle or operating heavy machinery." The Panel recommends that the term "antihistamines" should be prominently written and displayed in large letter print on the label of OTC daytime sedatives. Since OTC daytime sedatives contain ingredients similar to those in OTC nighttime sleep-aids, the Panel recommends many of the warnings established above for OTC nighttime sleep-aids. (See paragraph IIC1. above—*Conditions under which nighttime sleep-aids are generally recognized as safe and effective and are not misbranded.*)

The Panel recommends that Category III products be labeled as follows: *"Warning:* This product has not been demonstrated to be effective to the satisfaction of the Food and Drug Administration." In addition, the Panel is concerned about advertising claims of effectiveness for OTC daytime sedatives before clinical studies demonstrate effectiveness. The Panel concludes that such advertising is unfair to the consumer and should be banned during this period of testing.

REFERENCES

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(4) Downing, R. W., "Report to OTC Panel on Daytime Sedatives (Compoz Submission)," Draft of unpublished paper in OTC Volume 050048.[3]

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C. CATEGORIZATION OF DATA

1. *Conditions under which daytime sedatives are generally recognized as safe and effective and are not misbranded.*

*Active Ingredients*

After carefully reviewing all data available, the Panel is unaware of any active ingredients which are safe and effective and not misbranded.

*Labeling*

The Panel concludes that the warnings applicable to OTC nighttime sleep-aids are, in general, also appropriate for OTC daytime sedatives.

The Panel recommends the following general labeling for daytime sedative active ingredients to be generally recognized as safe and effective and not misbranded:

a. *Indications.* [Reserved].

b. *Warnings.* (1) "For adults only. Do not give to children under 12 years of age."

(2) "Do not take this product if pregnant or if nursing a baby."

(3) "Do not take this product if you are presently taking a prescription or other OTC drug, without consulting your physician or pharmacist."

(4) "If condition persists continuously for more than 2 weeks, consult your physician."

(5) "Take this product with caution if alcohol is being consumed."

(6) For products containing an antihistamine: *"Caution:* This product contains an antihistamine drug and may cause drowsiness. Avoid driving a motor vehicle or operating machinery."

2. *Conditions under which daytime sedatives are not generaly recognized as safe and effective or are misbranded.*

*Active Ingredients*

After carefully reviewing all data submitted, as well as additional evidence provided by consultants to the Panel and the results of an extensive literature search, the Panel concluded that the following OTC daytime sedative ingredients should either be removed from or not permitted on the market because of inadequate safety data relating to toxicity and excessive sedation, as well as no effectiveness data. The Panel found no scientific basis or even sound theoretical reasons for claimed effectiveness of these following ingredients to be used in OTC daytime sedatives:

*Active Ingredients*

Antihistamines
- Diphenhydramine hydrocholoride
- Doxylamine succinate

Bromides
- Ammonium bromide
- Potassium bromide
- Sodium bromide

Scopolamine Compounds
- Scopolamine aminoxide hydrobromide
- Scopolamine hydrobromide

Miscellaneous Compounds
- Acetaminophen
- Aspirin
- Salicylamide
- Niacinamide
- Thiamine hydrochloride

a. *Antihistamines.* The Panel has exhaustively reviewed the literature relating to the use of these antihistamines as OTC nighttime sleep-aids and daytime sedatives and conculdes that while the pharmacological effects of these compounds may be of value as nighttime sleep-aids as discussed earlier in this document, there are insufficient data to determine if these antihistamines are safe or effective as daytime sedatives for OTC use.

(1) *Diphenhydramine hydrochloride.* The Panel concludes that diphenhydramine hydrochloride cannot be generally recognized as safe or effective because there are no data to support clinical effectiveness as a daytime sedative product. The Panel notes that no submission was received for this ingredient as an OTC daytime sedative and that it has never been marketed for this activity. In addition, unlike the extensive clinical use of diphenhydramine as a nighttime sleep-aid, there are no clinical reports or clinical experience with this ingredient as a daytime sedative.

In the discussion above relating to diphenhydramine hydrochloride for use as a nighttime sleep-aid, the Panel has carefully set forth the action as well as side effects of this ingredient. From this discussion the Panel is unable to determine how this ingredient should be employed in OTC daytime sedatives. All of the discussion in the nighttime sleep-aid area tends to show diphenhydramine hydrochloride as an ingredient which will result in excessive drowsiness at therapeutic levels resulting either in sleep or decreased motor function, (e.g., inability to function properly when driving or operating machinery).

(2) *Doxylamine succinate.* The Panel concludes that doxylamine succinate cannot be generally recognized as either safe or effective because there are no data to support clinical effectiveness as a daytime sedative product. The Panel notes that no submission was received for this ingredient as an OTC daytime sedative and that it has never been claimed or marketed for this activity.

In the discussion above relating to doxylamine succinate for use as a nighttime sleep-aid, the Panel has carefully set forth the action as well as side effects of this ingredient. From this discussion the Panel is unable to determine how this ingredient should be employed in OTC daytime sedatives. All of the discussion in the nighttime sleep-aid area tends to show doxylamine succinate as an agent which will cause drowsiness, although only two clinical reports on the effectiveness of doxylamine as a nighttime sleep-aid have been found. No reports have been found on the use of this ingredient as a daytime sedative.

b. *Bromides (ammonium, potassium, sodium).* Based on the discussion above relating to bromides for use as a nighttime sleep-aid, the Panel concludes that they are unsafe as daytime sedatives. If taken over the period of time needed to reach therapeutic levels, severe toxic symptoms frequently occur. This is because bromides and chlorides are cleared from the kidney, but bromide clearance is slightly less efficient, so that the bromide level tends to build up.

The only submitted product suggests a dosage level of not less than 600 mg and not more than 1,800 mg per day of a combination of all three bromide salts. This product, which claims "calmative" action, sets no limit on the length of use of bromides. Yet, to use the bromides chronically without monitoring the patient's chloride balance and serum bromide is, in the Panel's view, not safe medical practice since small changes in chloride intake or small changes in renal function can lead to severe poisoning.

The Panel concludes that ammonium bromide, potassium bromide and sodium bromide, which act by displacement of body chloride, if taken in dosage levels presently recommended, do not act as daytime sedatives in a single dose. If taken over the period of time needed to reach therapeutic levels, severe toxic symptoms frequently occur. In addition, bromides readily cross the placental barrier, which might result in teratogenic effects such as mental retardation of the offspring.

The discussion of bromides in the nighttime sleep-aids section shows not only that the bromides are agents which, once they finally reach therapeutic levels, can cause excessive drowsiness, but also shows them to possess sufficient toxic characteristics to render them unsuitable for use as OTC daytime sedatives.

c. *Scopolamine compounds (scopolamine hydrobromide, scopolamine aminoxide hydrobromide).* The Panel concludes that these compounds are unsafe because of their extensive toxicity and are ineffective in presently marketed dosages.

In the discussion above relating to scopolamine for use as a nighttime sleep-aid, the Panel has carefully set forth the action as well as toxic effects of this ingredient. From this discussion the Panel is unable to determine how this ingredient should be employed in OTC daytime sedatives. All of the discussion in the nighttime sleep-aid area tends to show scopolamine compounds as agents which may result in extensive toxicity without any data to support their clinical effectiveness as daytime sedatives.

d. *Miscellaneous compounds (acetaminophen, aspirin, salicylamide, niacinamide, thiamine hydrochloride).* The Panel concludes that these compounds are irrational for use either singly or in combination as daytime sedatives. The Panel is unaware of any data for analgesics (acetaminophen, aspirin, salicylamide) or vitamins (niacinamide, thiamine hydrochloride) which support their use as daytime sedatives.

*Labeling*

As stated in the beginning of this section, the Panel has concluded that there appear to be no clear cut indications for the use of OTC daytime sedatives, and that the area of normal or relatively normal variations in mood is probably not an appropriate one for pharmacological intervention. An indication has not been clearly identified. All but one labeling claim has been placed in Category II. Therefore, claims such as "nervous irritability," "nervous tension headache," "simple nervousness due to common everyday overwork and fatigue," "a relaxed feeling," "calmative," "calming down and relaxing," "gently sooth away the tension," and "resolving that irritability that ruins your day," shall not be used. Only the labeling claims in Category III identified below may be used during the testing period provided.

3. *Conditions under 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 to permit final classification of the claimed active ingredients and labeling listed below:

*Active Ingredients*

Antihistamines
- Methapyrilene fumarate
- Methapyrilene hydrochloride
- Phenyltoloxamine dihydrogen citrate
- Pyrilamine maleate

a. *Antihistamines.* As noted in the discussion above, the Panel finds that there is little or no evidence that antihistamines possess desirable daytime sedative properties.

(1) *Methapyrilene hydrochloride, methapyrilene fumarate, pyrilamine maleate.* The Panel concludes that there is insufficient evidence to permit final classification of methapyrilene hydrochloride, methapyrilene fumarate and pyrilamine maleate for use in a daytime sedative product. The methapyrilenes appear in a number of marketed OTC products with daytime sedative claims. Pyrilamine appears in one OTC combination marketed product submitted to the Panel and, therefore, there are no data on the single ingredient.

In the discussion above relating to the methapyrilenes and pyrilamine for use as nighttime sleep-aids, the Panel has carefully set forth the actions as well as side effects of these ingredients. From these discussions, the Panel is unable to determine how these ingredients should be employed in OTC daytime sedatives. The Panel concludes that additional studies as outlined in the testing guidelines below are necessary to demonstrate the safety and effective-

ness of these ingredients as daytime sedatives. The Panel concludes that the dosage to be marketed during the testing period provided be limited to 25 to a maximum 50 mg single dose up to 4 times a day for methapyrilene (fumarate and hydrochloride) and to 10 to a maximum 25 mg single dose up to 4 times a day for pyrilamine maleate in studies of safety and effectiveness as daytime sedatives.

(2) *Phenyltoloxamine dihydrogen citrate.* The Panel concludes that there is insufficient evidence to permit final classification of phenyltoloxamine dihydrogen citrate for use in a daytime sedative product. The drug is currently promoted as a "calmative" in an OTC combination drug product. Since the drug is being marketed in a combination and no data are available on the ingredient alone as an OTC drug, the Panel has placed it in Category III as a daytime sedative.

In the discussion above relating to phenylotoloxamine dihydrogen citrate for use as a nighttime sleep-aid, the Panel has carefully set forth the actions as well as side effects of this ingredient. From these discussions, the Panel is unable to determine how this ingredient should be employed in OTC daytime sedatives. The Panel concludes that additional studies as outlined in the testing guidelines below are necessary to demonstrate the safety and effectiveness of this ingredient as a daytime sedative. The Panel concludes that the dosage to be marketed during the testing period provided be limited to 50 to a maximum 100 mg single dose up to 4 times daily for phenyltoloxamine dihydrogen citrate in studies of safety and effectiveness as a daytime sedative.

*Labeling*

It is the view of the Panel that there are insufficient data to permit final classification of the following labeling claim for an OTC daytime sedative product. Labeling for Category III shall only include "occasional simple nervous tension." This is the only labeling claim that may be used for such products during the 3-year testing period provided for the additional studies which are necessary and are described below. (See paragraph III D below—Data Required for OTC Daytime Sedative Ingredient Evaluation). The Panel further concludes that Category III products be labeled as follows: *"Warning:* This product has not been demonstrated to be effective to the satisfaction of the Food and Drug Administration."

D. DATA REQUIRED FOR OTC DAYTIME SEDATIVE INGREDIENT EVALUATION

The Panel is unable to determine a class of drugs that are safe and effective in the relief of anxiety-like symptoms for daytime OTC use. The Panel has classified the antihistamine ingredients methapyrilene, pyrilamine and phenyltoloxamine, currently marketed in combination products for daytime sedative use, in Category III. The Panel is of the opinion that if an indication for an appropriate population can be properly defined with labeling that clearly explains the use and limits of OTC daytime sedative products, then testing of appropriate active ingredients in a maximum dosage and container size might be feasible to demonstrate the safety and effectiveness of the ingredients. The Panel doubts, however, that any such effectiveness can be differentiated from the placebo effect. Were such testing to occur the Panel believes that the following guidelines should be considered for the evaluation of safety and effectiveness of an agent to be used as an OTC daytime sedative.

Any claimed ingredient(s) or labeling claim classified by the Panel as Category III should be evaluated using the concepts and methodology described below in the suggested guidelines.

1. *Minimum requirements to determine safety and effectiveness.* The active ingredient must be safe in the doses suggested on the labeling for OTC use. Safety should be evaluated using the current requirements for preclinical testing in animals as defined in 21 CFR 312.1(a)(2)6.a.

If an active ingredient is used as an OTC daytime sedative in doses sufficient to be effective, any central nervous system depression then becomes a potentially hazardous effect in addition to any therapeutic action that may be achieved. In the daytime, any deficit in the rate of reaction to stimuli, in alertness and/or motor coordination or in sensory discrimination may endanger the user of the drug. In the event that the user is the operator of a mechanical device or vehicle, he may endanger himself or other persons. These considerations weigh heavily in the opinion of the Panel because it is the view of the Panel that such deficits in motor and sensory function will be incurred if large enough doses of the active ingredient are employed to be effective in a daytime sedative. Thus, the effects of an active ingredient which are acceptable and even desirable from use of an OTC nighttime sleep-aid product may be dangerous and are certainly unacceptable for an OTC daytime sedative.

Evidence should be provided that the drug does not, in doses recommended, cause such impairment of motor or sensory performance that the subject may endanger himself or others. This applies to household appliances, the operation of machinery including surface, subsurface, or airborne vehicles, lathes, production-line equipment and the like. It includes the possibility of failure to react fast enough to an oncoming auto or other vehicle while crossing a street as a pedestrian. These cases are intended to be illustrative and not all-inclusive.

A drug used for self-treatment of symptoms such as "occasional simple nervous tension" must be more effective than a placebo. The Panel recognizes that such proof is difficult to demonstrate for an OTC daytime sedative because the "disease" or symptom is generalized and at best is ill-defined. The Panel is concerned that since such an episode is likely to be transient or at least poorly defined, anecdotal evidence of effectiveness has been the only type adduced. On the other hand, the usual clinical trials may not accurately reflect the actual effect of the drug.

Conventional drug trials, properly double-blinded, should demonstrate a dose-response effect and, hence, safety and effectiveness of the drug. If this cannot be achieved, proof of effectiveness becomes more difficult. In addition, there should be provision for large scale field studies in a well-defined target population requiring such OTC drug use, properly carried out by objective investigators. Such trials can be done by dispensing unlabeled drugs and placebos, including drugs known to be effective, to carefully selected control and experimental subjects. Information may be collected by questionnaire and/or interview. The interpretation of the complaint and of the effect (What is "nervousness"? and What constitutes relief of anxiety?) make inquiries of this type difficult but not impossible.

The problem of effectiveness is difficult because its appraisal involves subjective responses. These responses can be interpreted by statistical methods, but, first, they must be defined sharply and indications for the use of the drugs must be sharply defined too. Psychological scales exist and may be used in the clinical trials. Methods for setting forth criteria of anxiety, selecting subjects, and the use of rating scales of anxiety do exist as discussed in the volume edited by Levine et al. (Ref. 1), the FDA guidelines for evaluation of psychotropic drugs (Ref. 2) and in the Panel's testing guidelines described below.

2. *Assessment of suitable target population.* A number of appropriate subjects displaying mild to moderate symptoms of anxiety and tension who would most likely use such OTC products must be identified. The Panel is unable to determine any proper indications for the use of an OTC daytime sedative. A well-defined condition(s) existing in a suitable target population requiring such medication must be established before meaningful studies of effectiveness can be undertaken.

3. *Clinical studies in a suitable target population.* If a target population is identified, subjects should be studied for subjective effects for the proposed claims. Subjects should exhibit such anxiety-like symptoms within the target population expected to take the drug. The Panel suggests several well-controlled studies utilizing two major approaches: (1) Continuous treatment studies of 2-week duration, where the drug is continuously given about 3 to 4 times daily, using between-patient design. The patient evaluates his emotional state daily as well as more intensively weekly, and the physician evaluates the patient also at weekly intervals. (2) Occasional use studies, in which the drug is used as needed, i.e., only occasionally, for temporary symptoms. The patient evaluates his or her emotional state before and after he takes his medication for a given symptom occurrence.

The physician will monitor the patient at infrequent intervals. In this latter group of studies a between-patient or a within-patient (crossover) design may be utilized. Although not required, a positive control could be used for measuring the activity of the drug against that of a known psychotropic drug. Such addition would also serve as a yardstick of the appropriateness and sensitivity of the study population for detecting drug-placebo differences. If several doses of a drug are to be studied, a larger number of groups is required. For instance, if a combination containing two ingredients (A+B) is studied, the design should include four separate groups, one taking placebo, one taking A, one taking B and one taking A+B. Subjects are to be assigned by systematized randomization with packaging and coding of the drug on an individual patient basis rather than on a treatment group basis. The Panel is concerned that the integrity of the study be maintained, that subjects are not able to determine drug from placebo, since the findings are heavily dependent on subjective responses.

The variables to be investigated include the subject's estimate of relief for the claimed effect and a report of any side effects.

4. *Guidelines for studies of daytime sedatives.* a. *Objectives.* The overall objectives are: (1) to determine the effects of the drug in individuals with mild to moderate symptoms of anxiety and tension likely to use such an OTC drug, (2) to determine the subjects' estimate of improvement for the claimed symptoms, an estimate of how well they fell after drug treatment and (3) to determine any preferences the subjects may have between treatments (drug versus positive control or placebo).

b. *Sample considerations.* Subjects should exhibit mild to moderate symptoms as suggested for the labeling claims, e.g., simple nervous tension. Subjects with severe or chronic anxiety-like symptoms are not candidates for self-medication, since they should be under the supervision of a physician.

A variety of populations differing as to age, sex, diagnostic categories, social class, treatment setting, previous treatment, etc., may be studied. Within each study (or subgroup in studies of sufficient size), subjects should be selected to be as homogeneous as possible regarding the variables above. Patients with strong sociopathic trends, alcoholism, organic brain disorder, character disorder, evidence of schizophrenia or glaucoma and patients in need of analgesic, hypnotic, or anticholinergic medication should be excluded. In any case, full reporting of subjects' characteristics is necessary to allow for adequate interpretation of results. Exclusions should be stated.

c. *Sample size.* The study should use separate large groups containing 40 to 80 subjects per group. In a study comparing separate groups, a minimum of two groups (drug and placebo) are necessary. A large number of groups are required if several doses of a drug are studied or if a combination of several ingredients are evaluated, each ingredient should be compared to the combination and a placebo. This sample is about twice the size recommended for anti-anxiety prescription drug testing (Ref. 1). This large sample size is needed because the effects being investigated are expected to be small in relation to those found for psychotropic drugs.

d. *Setting.* Environmental variation in influences should be decreased as much as possible in each study. Different treatment environments may be used which should be similar to those likely to be found among users (consumers) of such OTC products.

e. *Investigators.* The investigators should be experienced in evaluating drugs affecting the central nervous system and in the conduct of clinical trials. The Panel recommends that evidence for the qualifications of investigators should be provided to the FDA prior to onset of any study. The Panel has recommended this (1) to ensure a high quality and reliability of the investigations and (2) to protect the health of human subjects who participate in such studies.

f. *Design.* Of primary importance are well-controlled studies designed to investigate the safety and effectiveness of the drug as a daytime sedative. Special consideration should be given to controls, duration of study, dosage, and design which do not interfere with validity (biostatistical consulation is recommended) to accommodate greater variations in settings, and subjects. A washout period may be applicable in the limited treatment clinical studies, but may be omitted in the occasional-use and consumer survey studies when a broader experience with the drug is being gathered.

g. *Dosage.* A flexible dosage schedule should be used with increasing amounts up to the dosage level proposed to be available for OTC drug use.

h. *Duration.* The duration of studies may vary from 1 to 2 weeks. In most cases the drug will be taken for temporary relief and occasional use, and therefore, long-term studies are not absolutely essential. However, the Panel believes that such studies are advisable.

i. *Assessment.* Activity as a daytime sedative should be determined by standard validated rating scales. Ratings should be repeated at intervals during the treatment regimen in addition to a baseline evaluation. Determination of safety and effectiveness should include subjective reports from patients or subjects and objective reports by professional observers, e.g., observations of a nurse. Assessment measurements should also include appropriate scales to distinguish between sedation and occasional nervous tension.

5. *Suggested studies for evaluation of daytime sedatives.* The Panel concludes that any one of the following studies could be performed to demonstrate the safety and effectiveness of a daytime sedative:

a. *Continuous treatment study.* A study of 2 weeks could be performed in individuals who use these products on a continuing basis. Patients should be evaluated by a physician frequently, in the following sequence: previous to beginning the study, perhaps every 3 days during the study, and at the completion of the study. Patients should also evaluate themselves with global improvement measures and more circumscribed rating scales.

b. *Occasional use study.* Such a study could be performed in patients with symptoms requiring the drug for occasional use only, perhaps once or twice a week. In these cases, a patient could maintain a personal log with a subjective evaluation of symptom relief. In such a study, global ratings and mood scales (adjective check test) may represent relevant outcome criteria. In such a study, the subject would be evaluated by a physician on a more infrequent basis.

6. *Minimum data required for classification as a Category I ingredient.* The Panel recommends that the testing guidelines above be used; they are adopted from the recent FDA guideline draft on psychotropic drugs (Ref. 2) as well as on the recently published book by Levine et al. (Ref. 1).

The Panel recommends that at least two studies using each of the two suggested designs be carried out initially. Further studies should then be carried out using the study type which was most sensitive in detecting drug-placebo differnces in the original four studies. This is necessary to demonstrate that any observed differences in treatment effects were not of a spurious nature.

If the four original studies should all be unable to differentiate drug and placebo, further testing would seem inadvisable. On the other hand, if all four original studies showed clear-cut drug-placebo differences, future studies would also not be needed and the particular drug in question could be moved from Category III to Category I.

REFERENCES

(1) "Principles and Problems in Establishing the Efficacy of Psychotropic Agents," Edited by Levine, J., B. Schiele, and L. Bouthilet, United States Public Health Service Publication No. 2138, (1971).

(2) "Guidelines for the Conduct of Clinical Trials: FDA Guidelines for Psychotropic Drugs," *Psychopharmacology Bulletin*, 10:70–91, 1974.

E. COMBINATIONS OF ACTIVE INGREDIENTS

As noted earlier in this document, the Panel has not identified an indication or appropriate active ingredients for use in OTC daytime sedatives. If a properly defined indication can be identified and appropriate active ingredients found, the Panel refers to the guidelines and criteria for combinations of active ingredients for nighttime sleep-aids. (See paragraph II E above—Combinations of Active Ingredients.)

The discussion in the nighttime sleep-aids section relating to combinations of nighttime sleep-aids and nonnighttime sleep-aid ingredients would also be applicable to daytime sedative products. There was one combination containing the antithistamine phenyltoloxamine dihydrogen citrate, an analgesic and caffeine, in a submitted product which

claimed both calmative action and enhanced pain relief. However, neither that submission nor any other data reviewed by the Panel indicated that OTC analgesics have sedative action. In fact, the particular combination submitted usefully divided its analgesic and "calmative" claims and attributed the calmative action only to phenyltoloxamine (Ref. 1). As to the claimed enhancement of the analgesic effect which results when the analgesic is combined with an antihistamine, the Panel defers to the OTC Internal Analgesic Panel for such a determination. The Panel places the combination in Category III.

REFERENCES

(1) OTC Volume 050031.[6]

## IV. STIMULANTS

### A. GENERAL DISCUSSION

The Panel is aware of the use of either prescription drugs (e.g., amphetamines, desoxyephedrine) or OTC drugs (e.g., caffeine) by many individuals to promote wakefulness and to decrease the sense of fatigue and boredom in performing tedious work over rather long periods of time. Such drugs are referred to as stimulants and are used to increase mental alertness. For example, caffeine is commonly used as an aid to automobile driving, especially for the relief of the phenomenon "highway hypnosis" encountered during extensive periods of continuous driving. Currently marketed OTC products are promoted with such claims as "keep alert," "restore mental alertness," and "for fast pick-up."

The Panel believes that a suitable adult target population exists which can benefit from the occasional use of safe and effective OTC stimulant drugs. In cases where mental alertness or motor performance is necessary, such drugs can modify fatigue states to allow successful completion of a required task. The Panel is of the opinion that use of such OTC products by individuals under 12 years of age should only be under the advice and supervision of a physician.

The Panel concludes that an ideal OTC stimulant preparation must be able to produce enhanced motor performance when such performance is reduced because of fatigue or drowsiness. The therapeutic effect should be of sufficient duration to be useful in accomplishing a particular task. For example, the drug should permit an automobile driver to maintain normal performance in completing a reasonably short journey to a stopping place. Hence, such products are for ocasional use only and never for more than 1 to 2 weeks except under the advice and supervision of a physician.

### B. SAFETY AND EFFECTIVENESS

The Panel concludes that the ideal OTC stimulant preparation should produce stimulation without untoward physiological effects on the central nervous system or the cardiovascular system or other acute toxic signs. Such undesirable effects would include an appreciable number of abnormalities of rate and/or rhythm of the heart or of respiration, or excitement or other undue disturbances of central nervous system function. In general, side effects that follow use of the drug should not be of such a degree or quality as to offset the beneficial effects of the drug. For example, excessive nervous system stimulation to an extent that would exceed the effect required to reduce fatigue could reduce the efficiency of motor vehicle operator. The drug should produce enhanced performance without leading to a dangerous and unanticipated letdown after the therapeutic effect is achieved. There should be no distressful effect upon peripheral nervous functions, such as an obvious tremor or incoordination caused by the stimulant. There should be no interference of a significant degree with the normal pattern of sleep, including the quality, distribution in time, and the quantity of REM sleep. REM or D-state is rapid-eye-movement sleep associated with dreaming. When the amount of such sleep is reduced, it may lead to excess restlessness or irritability in the waking state. The drug should be for occasional use of not more than 2 weeks, and there should neither be tolerance nor dependence after such use. There should be a safe margin between the toxic and therapeutic doses of the drug. There should be no interactions of a dangerous or unpleasant nature between the drug and the other commonly employed drugs, foods or beverages when these are taken concomitantly.

### C. CATEGORIZATION OF DATA

1. *Conditions under which stimulant products are generally recognized as safe and effective and are not misbranded.*

*Active Ingredient*

The Panel concludes that caffeine is safe and effective for use as a stimulant when used in the recommended oral dose of 100 to 200 mg not more often than every 3 to 4 hours.

The Panel has not encountered any reports of fatal accidents after oral ingestion of caffeine and concludes that the incidence of fatal toxicity is low. The fatal dose for man is probably far greater than recommended doses since ingestion of up to 10 gm was followed by complete recovery in 6 hours (Ref. 1). With doses of 1 gm, insomnia, anxiety, irritability, muscle twitching, headache and nausea may be experienced. Palpitations, tachycardia and cardiac irregularity may also occur (Ref. 2).

Death was reported after intravenous administration of 3.2 gm. In such cases, there may well be other factors. Too rapid injection of almost any drug can cause cardiorespiratory collapse and death. A review of acute and chronic toxicity with regard to caffeine has been prepared by Peters (Ref. 2). Severe poisoning causes cardiovascular collapse, including a fall in blood pressure. Vomiting and convulsions have followed oral doses of 10 gm of caffeine with complete recovery in 6 hours.

Chronic ingestion of caffeine in larger than recommended doses can lead to "habituation" which is a mild form of drug addiction. When this occurs, caffeine, usually taken in the form of beverages, is required to feel "normal." Withdrawal symptoms are not severe or life-threatening (Refs. 3, 4, and 5). However, the Panel recommends that products containing caffeine should not include claims such as "non-habitting-forming" in their labeling. Caffeine affects the pattern of REM sleep (rapid-eye-movement sleep, "D state" sleep) but not the total amount of REM sleep (Ref. 6).

The Panel notes that coffee (or strong tea) contains about 100 mg caffeine per cup, the same amount as the usual recommended dose of caffeine currently marketed in OTC preparations. The literature contains much information about studies on coffee drinkers vs. noncoffee drinkers.

The stimulating effect of caffeine (100 to 200 mg) on motor performance has been quite consistently reported by many investigators using a variety of experimental designs and tests of performance. The drug is most effective in the presence of fatigue, restoring alertness and the ability to perform tasks requiring muscular coordination with greater facility and less error. Reports of such effects can be explained on the basis of central nervous system (brain) stimulation and do not depend on peripheral effects, such as direct effects on the retina, improvement in "night vision," or the like (Refs. 7 through 10). In large doses, caffeine can stimulate respiration, but drugs are not ordinarily used for this effect in present-day clinical medicine (Ref. 11).

Chemically, caffeine is 1,3,7-trimethylxanthine. It is an alkaloid that occurs in plants (coffee, tea, cocoa, cola) widely distributed around the world. Because of its ubiquitous use and availability from nondrug sources, the Panel felt that its assessment of the compound should be based on an "in-depth" review of its pharmacology.

Approximately 7 million kg of caffeine in coffee are consumed each year in the United States (Ref. 12). As mentioned above, 1 cup of coffee contains about 100 to 115 mg of the drug. The major pharmacological effects are on the central nervous system and the cardiovascular system. It is also diuretic and stimulates gastric secretion.

Caffeine stimulates the cerebral cortex and medullary centers. In usual doses, it causes wakefulness and alertness. As a beverage form, caffeine in coffee (among others) has been habit-forming in a proportion of the population. This "habituation" is probably a weak form of "addiction" in that differences may be detected between persons who use coffee regularly and those who do not use it at all. Goldstein and colleagues showed that chronic coffee drinkers given decaffeinated coffee showed sleepiness and irritability whereas noncoffee drinkers given caffeine-containing coffee showed upset stomachs and jitteriness due to caffeine. Users of coffee felt increased alertness and "contentedness" when given caffeine in their "coffee" (Ref. 3). In a related study conducted by questionnaire, it was found that chronic users of coffee did

not experience as much wakefulness due to coffee as did nonusers. Moreover, they experienced unpleasant symptoms when morning coffee was omitted (Ref. 4). Additional evidence for an addiction of some degree is the finding that sudden withdrawal of caffeine produced severe headache in a majority of trials among volunteer subjects. The headache produced in these young adults was relieved by aspirin, but more efficiently by caffeine (Ref. 5.) Many of the persons studied by these authors were subject to migraine headaches. It is noteworthy that caffeine, generally in large doses, is used in the treatment of migraine.

The stimulatory effect of caffeine on motor performance has been quite consistently reported. The clearly effective central stimulation caused by caffeine ingestion has been supported by carefully designed studies (Refs. 3, 4, 7, 8 and 13).

In a comprehensive review of the effects of stimulant drugs, Weiss and Laties (Ref. 9) concluded that caffeine can enhance "a wide range of behavior * * * all the way from putting the shot to monitoring a clock face." There is evidence from a variety of studies that nervousness, headache, and irritability, for example, may accompany the use of large doses, 240 mg of caffeine and above. There seems to be no evidence of serious types of addiction, and their conclusion is that the incident of habituation is quite low.

Studies that measure ability to perform simulated driving tests with adequate lighting and in conditions of reduced lighting were submitted by one of the manufacturers of a drug containing caffeine (Ref. 10). All responses that were favorable may be explained on the basis of enhanced central nervous system performance and did not seem to involve improvement in vision at the level of the orb itself, that is, cornea to retina. In so far as any may be demonstrated, effects on "night vision" are probably due to enhanced alertness (Ref. 10).

Caffeine has a stimulant action on the heart and can increase cardiac output. Sollmann (Ref. 14) states that methylxanthines (which include caffeine) are useful potentially in acute heart failure, but the effects appear to be manifold and unpredictable. Theophylline, another xanthine, is said to be more effective than caffeine in stimulating the output of the failing heart by a direct inotropic effect.

For OTC oral use as a stimulant, citrated caffeine is currently available in 60 and 120 mg oral tablets. Caffeine is also added to headache remedies containing salicylates and acetaminophen; and to ergotamine for the relief of migraine. The Panel defers to the OTC Internal Analgesic Panel the determination of the safety and effectiveness of caffeine for the relief of headache or migraine.

Caffeine and sodium benzoate are given also by physicians in dosages of 0.5 to 1.0 gm for subcutaneous or intramuscular use as a central nervous system stimulant. Small doses seem to enhance alertness and ability to perform learned tasks. Large doses can stimulate respiration. Caffeine and other xanthines are often used as acetate, benzoate, or salicylate salts. Forming the salt simply increases solubility; it does not affect action. Addition of sodium benzoate probably assists absorption in the acid pH of the stomach, although the nonionic form would probably be well absorbed from the intenstine. In any case, the drug appears to be well absorbed when given by mouth (Ref. 15).

The exact mechanism of action of caffeine is not precisely known.

The problem of mutagenicity of caffeine has been reviewed by the Panel. There is evidence that concentrations of caffeine many times higher than would ordinarily be found in human or animal tissues cause certain mutations in the bacterium *Escherichia coli*, and in the fungus *Ophiostoma multiannulatum* (Refs. 16 and 17). Caffeine has also been reported to induce chromosome aberrations in onion root tips and in human cells in vitro (Refs. 18 and 19). Very careful studies in mammals have failed to reveal evidence of mutagenicity (Refs. 20 and 21).

Caffeine causes chromosome breakage in the human lymphocyte in tissue culture (Refs. 20, 22, 23 and 24) but no evidence for this action in vivo in man or other mammals has been found (Ref. 20). The mechanism of the chromosome breakage has been studied, but not explained (Ref. 25). Lymphocytes from human volunteers ingesting 800 mg caffeine daily (equivalent to 8 cups of coffee) for 30 days showed no increase in chromosome damage when the cells were placed in culture. In the human volunteers, the peak plasma levels were 29.6 mcg/ml of caffeine, over 3-fold greater than any preexperiment level. There was no increase in chromosome breakage when these cells were cultured.

HeLa cells were exposed to concentrations of caffeine in the medium about 10 times greater than that found in vivo in plasma of human subjects drinking 8 cups of coffee per day (800 mg caffeine). There was no increase in chromatid breaks in cultures studied through 48 generations of the HeLa cells (Ref. 26).

Looking for mutagenic indications, different concentrations of caffeine in vitro were studied for an antimitotic action on cell division of human lymphocytes stimulated to divide by phytohemagglutinin, a plant product. Concentrations of caffeine in the medium that interfered with cell division were about 100 fold greater than would be encountered in human tissues after an intake of a usual dose of caffeine or right after drinking a cup of strong coffee (approximately 100 mg caffeine) (Ref. 27). In one study, the effects of three xanthines, theobromine, theophylline, and caffeine were studied for their effectiveness in blocking mitosis of human lymphocytes in 72-hour culture. High concentrations of caffeine ($10^{-3}$ to $10^{-4}$ molar) were needed to demonstrate cytostatic and antimitotic effects. It was concluded that any mutations in man caused by caffeine at concentrations ordinarily achieved would have to occur at a rate too low to be detectable (Ref. 28).

The suspected role of caffeine in mutagenesis and also teratogenesis has led to a scrutiny of this substance, a scrutiny that is almost certainly more intensive and extensive that that conducted for any other commonly ingested food or drug. Teratogenicity of caffeine can be detected in rats if sufficiently high doses are given; these are of the order of 250 mg/kg and would be equivalent to 100 cups of coffee containing 125 mg of caffeine each. Metabolism of caffeine in man is rapid, and it may be that this protects man from teratogenic effects (Ref. 29). A review of the mutagenic effects, in particular dominant lethal tests, shows less evidence for organisms higher than bacteria, fungi, and higher plants (Ref. 29).

The safety of coffee has been questioned recently by a drug surveillance group (Ref. 30). The findings of the group suggested an increase of serious heart disease among heavy coffee drinkers. However, there was no positive association among tea drinkers. This would appear to exclude implication of caffeine present in both coffee and tea. The report has been criticized by others who indicate further evidence is needed to demonstrate a role of coffee in the genesis of cardiovascular disease (Ref. 31). These other investigators found no evidence for the role of coffee in any increased risk of death because of cardiovascular disease in a large, well-known (Framingham study) prospective study of factors involved in the genesis of coronary heart disease (Ref. 32). No generally accepted evidence would implicate caffeine as a danger in this regard. Furthermore, another recent publication using large numbers of subjects has not supported the contention about coffee drinking promulgated by the Drug Surveillance Group (Ref. 33). The Panel concludes that there is inconclusive evidence linking coffee and/or caffeine to cardiovascular disease. In another study of paired-control patients, there was a higher incidence of myocardial infarction with very high consumption of coffee. Caffeine was implicated only indirectly, on the basis of elevation of serum lipids evoked by caffeine administration (Ref. 34). In a study of 1,700 men between the ages of 40 and 55 years (Ref. 35), there was said to be an "increasing incidence of angina pectoris and of myocardial infarction with survival" among men consuming 5 or more cups of coffee a day. Curiously, the death rate was highest among those who took no coffee or consumed 5 or more cups of coffee per day. There is no level of significance given and the number of deaths is small.

In contrast to the irritating qualities of many coffee extracts, caffeine itself does not seem to cause irritation of the gastrointestinal tract in the usual doses. This is an advantage when the drug is used for its stimulant properties.

The observations that suggest some central stimulation that leads to, or is

associated with, a mild form of addiction to caffeine raise questions about long-term use. The Panel questions if subjects are paying some price not yet detected. This appears to be true for most hypnotics in that we now know that there are, at the least, changes in the amount of rapid-eye movement (REM) sleep and that some kind of deficit is built up. This occurs in addition to the separate risk of addiction to the hypnotic itself. In the case of stimulants used to enhance the performance of school children deemed hyperactive, Sroufe and Stewart have suggested that there may be no persistent effect of drug therapy upon these children, but that they become dependent upon the stimulant drugs to maintain a level of performance not much different from pre-drug performance (Ref. 36).

In summary, the panel believes that caffeine as an OTC stimulant appears to be safe and effective. It is reasonably nontoxic in that fatal doses for man are estimated to be greater than 10 gm by mouth.

Caffeine has the ability to produce a low grade of "addiction" that is commonly referred to as "habituation," and has been most extensively studied in coffee drinkers. The Panel believes this is not a dangerous problem and does not believe that a warning regarding habituation is necessary. However, the Panel recommends that stimulant products containing caffeine should not include in the labeling a suggestion such as "non-habit-forming."

Caffeine has not been shown to be mutagenic to man or mammals, although there are some weak mutagenic effects that can be demonstrated in certain bacterial viruses. The claim that coffee drinkers have more heart disease than noncoffee drinkers is not proven to the satisfaction of the Panel and is not relevant because it does not extend to caffeine. The claim relating to heart disease has involved coffee and has "absolved" tea drinkers (who ingest caffeine in their tea). The possibility that extensive daily caffeine intake (tablets, coffee, cola drinks, etc.) may mimic neurotic anxiety reaction has recently been raised (Ref. 37). Labeling will therefore include a warning to this effect.

The addition of substances to caffeine preparations as marketed should be closely scrutinized. Since the addition of proprietary flavors such as menthol and peppermint or sugars or their substitutes encourages ingestion by children, they serve to enhance the possibility of poisoning. The Panel opposes inclusion of these substances. Talc should also be removed from any preparations intended for human consumption. It is nonessential, and its safety is in question. Only talc that contains no asbestos fibers should be permitted to enter the body by any route. To ensure this, the source and composition of each talc lot need to be known. There is no generally available or "official" test for the presence of asbestos fibers in talc insofar as the Panel knows. Evidence is at hand that asbestos fibers can cause chronic respiratory disease, adenocarcinoma of the lung, and mesothelioma of the pleura and peritoneum when such fibers are inhaled. There is also evidence that ingestion of asbestos by animals can cause cancer. (See paragraph II F above—Inactive Ingredients.)

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*Labeling*

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

a. *Indications.* "Restores mental alertness or wakefulness when experiencing fatigue or drowsiness."

b. *Warnings and/or cautions.* Labeling should contain the following warnings:

(1) *"Caution:* Do not exceed recommended dose since side effects may occur which include increased nervousness, anxiety, irritability, difficulty in falling

asleep and occasionally, disturbances in heart rate and rhythm called palpitations."

(2) "For occasional use only. If fatigue or drowsiness persists continuously for more than 2 weeks, consult a physician."

(3) "For adults only. Do not give to children under 12 years of age."

(4) The Panel recommends that an OTC stimulant product containing caffeine should also include the following warning:

"*Contains caffeine.* Do not take this product with large amounts of caffeine containing beverages such as coffee, tea or cola drinks." The Panel believes such a warning is necessary since an average cup of coffee or strong tea contains an amount of caffeine about equal to that in the average dose of OTC products. Certain cola drinks also contain a significant amount of caffeine and should also be included in the warning.

2. *Conditions under which stimulant products are not generally recognized as safe and effective or are misbranded.* After carefully reviewing all data submitted, as well as additional evidence provided by the FDA and consultants to the Panel and the results of an extensive literature search, the Panel found no scientific basis or even sound theoretical reasons for claimed effectiveness of a number of ingredients used in OTC stimulants. In addition, certain labeling claims are clearly misleading. For example, statements or suggestions that stimulants and stimulant combination products (with nonstimulant ingredients) "increase sensual pleasure" are undocumented claims in the presently available literature and are, therefore, unacceptable to the Panel.

The Panel concludes that stimulant products containing the following ingredients should be removed from the market unless further scientific testing supports their use, because there are no data to support their use alone or in combination as a stimulant. The Panel has determined that these ingredients have no action as a stimulant nor do they contribute to the claimed effectiveness of a stimulant (e.g., caffeine) as an ingredient in a combination product.

*Active Ingredients*

Combinations of Caffeine with Nonstimulant Active Ingredients:

Ammonium chloride
Ginseng
Vitamins

a. *Ammonium chloride.* The Panel concludes that a combination product in which caffeine is combined with ammonium chloride is not rational for use as an OTC stimulant preparation. The Panel is unaware of any data which demonstrate a role for use of ammonium chloride, either alone or in combination with caffeine as a stimulant.

The Panel is aware that products containing ammonium chloride and caffeine are promoted for premenstrual tension with the claim "helps relieve premenstrual symptoms: swelling, weight gain and fatigue."

The Panel, after a review of the literature, has not found acceptable evidence that the use of ammonium chloride and caffeine is rational for the purpose of reducing fatigue. Caffeine alone may be expected to increase rather than decrease associated nervousness. The use of ammonium chloride for other claims has been deferred by the Panel to the OTC Internal Miscellaneous Panel as to the safety and effectiveness of this ingredient.

b. *Ginseng.* The Panel concludes that there is no rationale for adding ginseng to a stimulant drug.

The Panel found no data to suggest a stimulant action for ginseng or for potentiation or enhancement of the stimulant effect of caffeine. After an extensive review of the available scientific literature, the Panel found no reasonable studies or supporting documentation to suggest ginseng in combination with caffeine to affect or enhance sexual drives or awareness.

c. *Vitamins.* The Panel concludes after an extensive review of the available scientific literature, that there is no acceptable medical rationale for combining vitamins (especially Vitamin E) with caffeine. The Panel further makes reference to the discussion of vitamins in the section on nighttime sleep-aids (See II above—*Nighttime Sleep-Aids.*) The Panel found no acceptable rationale to explain the combination of caffeine and vitamins.

The Panel defers to the OTC Vitamin, Mineral and Hematinic Drug Product Panel on the safety, effectiveness and labeled claims for vitamins. The Panel notes that the proper functioning of all cells requires an adequate intake of all vitamins (water-soluble and fat-soluble). It is misleading to assume or propose that individuals consuming stimulant drugs have certain deficiencies. There is virtually nothing in the current medical or pharmacological literature to support the inclusion of selected vitamins in OTC stimulants. In addition, the small amounts of water-soluble vitamins contained in OTC stimulants are virtually homeopathic due to the fact that vitamins are rapidly excreted in the urine. This provides no rationale to support the inclusion of these ingredients in products designed to provide CNS stimulation.

The Panel strongly believes that polypharmacy and a "shotgun" approach to treatment of symptoms with fixed-dose combinations have no rational therapeutic basis.

The value of the placebo effect in the management of psychosomatic illness and minor neuroses is obvious. It is extremely doubtful however, that the inclusion of vitamins in a self-prescribed stimulant enhances any placebo effect these products may confer.

*Labeling*

In one submission, a combination product containing caffeine with ginseng is claimed to "increase sensual awareness and pleasure." Although not stated explicitly, it is apparent to the Panel that the intent of this labeling is to equate sensual awareness and pleasure with increased sexual capability and pleasure. The utility of ginseng has been discussed previously where is was stated that no evidence of enhanced sexual experience or potency has been found. In the case of caffeine, the Panel is unaware of any studies that clearly show an enhancement of sensual or sexual experience by the ingestion of this drug. Certainly no submissions to the Panel deal with this indication. In the absence of any positive evidence for an effect an sensual or sexual experience, the Panel objects to labeling that states or implies "increases sensual pleasure."

In the same submission, caffeine with vitamin E is claimed to "increase sensual (sexual) awareness." The Panel, after an extensive review of the available medical and scientific literature, found no reasonable supporting documentation to even suggest that vitamin E in combination with caffeine affects or enhances the sensual (sexual) experience in man. In the Panel's opinion, neither ingredient has been shown to affect sexual experience in man and therefore such claims are false and misleading.

The Panel also concludes that labeling claim(s) that suggest a product containing caffeine is "non-habit-forming" are misleading and should not be allowed. Prolonged ingestion of caffeine especially in larger than recommended doses can lead to habituation. (See paragraph IV C 1. Conditions under which stimulant products are generally recognized as safe and effective and are not misbranded.

3. *Conditions under 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 to permit final classification of the claimed labeling listed below:

*Labeling*

The question of whether a stimulant such as caffeine "enhances performance" in the nonfatigued state cannot be answered definitively at this time. Although there are some suggestions, but not proof, that this may be true, additional evidence in well-controlled trials would be necessary for such an indication to be included in the labeling. If such proof is obtained, it must also be demonstrated, in the same human subject, that no side effects accompany enhanced performance. In the case of caffeine, such side effects would include, among others, tremor, palpitations, and nervousness.

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 (5 U.S.C. 553, 554, 702, 703, 704) and under authority delegated to him (21 CFR 2.120), the Commissioner proposes that Subchapter D of Title 21 of the Code of

Federal Regulations be amended by adding new Parts 338, 339, and 340 to read as follows:

## PART 338—NIGHTTIME SLEEP-AID PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions



Subpart B—Active Ingredients



Subpart C—[Reserved]

Subpart D—Labeling



AUTHORITY: 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), (5 U.S.C. 533, 554, 702, 703, 704).

### Subpart A—General Provisions

**§ 338.1 Scope.**

An over-the-counter nighttime sleep-aid product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this Part 338 and each of the general conditions established in § 330.1 of this chapter.

**§ 338.3 Definition.**

As used in this part, "nighttime sleep-aid" is an agent which helps to reduce difficulty in falling asleep including delayed sleep, frequent awakenings, light sleep or reduced duration of sleep.

### Subpart B—Active Ingredients

**§ 338.10 Nighttime sleep-aid active ingredients. [Reserved]**

**§ 338.40 OTC product container.**

The OTC product container shall contain not more than any established maximum quantity for an applicable active ingredient identified in § 338.10.

### Subpart C—[Reserved]

### Subpart D—Labeling

**§ 338.50 Labeling of nighttime sleep-aid products.**

(a) *Indications.* The labeling shall identify the product as a "nighttime sleep-aid" to "reduce difficulty in falling asleep." Labeling may also include the phrases: "Helps fall asleep" and "For relief of occasional sleeplessness".

(b) *Directions for use.* The labeling of the product contains the recommended dosage and appropriate directions under the heading "Directions", e.g., once daily at bedtime broken down by age groups, if appropriate, followed by "or as directed by a physician".

(c) *Warnings.* The labeling of the product contains the following general warning(s) under the heading "Warnings":

(1) "For adults only. Do not give to children under 12 years of age."

(2) "Do not take this product if pregnant or if nursing a baby."

(3) "Do not take this product if you are presently taking a prescription drug or other OTC drug, without consulting your physician or pharmacist."

(4) "If condition persists continuously for more than 2 weeks, consult your physician. Insomnia may be a symptom of serious underlying medical illness."

(5) "Take this product with caution if alcohol is being consumed."

(6) For products containing an antihistamine: *"Caution:* This product contains an antihistamine drug."

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## PART 339—DAYTIME SEDATIVE PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions



Subpart B—Active Ingredients



Subpart C—[Reserved]

Subpart D—Labeling



AUTHORITY: 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); (5 U.S.C. 553, 554, 702, 703, 704).

### Subpart A—General Provisions

**§ 339.1 Scope.**

An over-the-counter daytime sedative product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this Part 339 and each of the general conditions established in § 330.1 of this chapter.

**§ 339.3 Definition.**

As used in this part, daytime sedative is an agent which claims relief of occasional nervous tension.

### Subpart B—Active Ingredients

**§ 339.10 Daytime sedative active ingredients. [Reserved]**

**§ 339.40 OTC product container.**

The OTC product container shall contain not more than any established maximum quantity for an applicable active ingredient identified in § 339.10.

### Subpart C—[Reserved]

### Subpart D—Labeling

**§ 339.50 Labeling of daytime sedative products.**

(a) *Indications.* The labeling shall identify the product as a "daytime sedative".

(b) *Directions for use.* The labeling of the product contains the recommended dosage and appropriate directions under the heading "Direction", e.g., once 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 following general warning(s) under the heading "Warnings":

(1) "For adults only. Do not give to children under 12 years of age".

(2) "Do not take this product if pregnant or if nursing a baby".

(3) "Do not take this product if you are presently taking a prescription drug or other OTC drug, without consulting your physician or pharmacist".

(4) "If condition persists continuously for more than 2 weeks, consult your physician".

(5) "Take this product with caution if alcohol is being consumed."

(6) For products containing an antihistamine: *"Caution:* This product contains an antihistamine drug and may cause drowsiness. Avoid driving a motor vehicle or operating machinery."

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## PART 340—STIMULANT PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions



Subpart B—Active Ingredients



Subpart C—[Reserved]

Subpart D—Labeling



AUTHORITY: 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); (5 U.S.C. 553, 554, 702, 703, 704).

### Subpart A—General Provisions

**§ 340.1 Scope.**

An over-the-counter stimulant product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this Part 340 and each of the general conditions established in § 330.1 of this chapter.

**§ 340.3 Definition.**

As used in this part, "stimulant" is an agent which restores mental alertness or wakefulness during fatigue or drowsiness.

### Subpart B—Active Ingredient

**§ 340.10 Stimulant active ingredient.**

The active ingredient of the product consists of caffeine when used within the dosage limit established: adult oral dosage 100 to 200 mg not more often than every 3 to 4 hours.

### Subpart C—[Reserved]

### Subpart D—Labeling

**§ 340.50 Labeling of stimulant products.**

(a) *Indications.* The labeling shall identify the product as a "stimulant" that "restores mental alertness or wakefulness when experiencing fatigue or drowsiness".

(b) *Directions for use.* The labeling of the product contains the recommended dosage and appropriate directions, identified in § 340.10, under the heading "Directions" followed by "except under the advice or supervision of a physician".

(c) *Warnings.* The labeling of the product contains the following warning(s) under the heading "Warnings":

(1) *"Caution:* Do not exceed recommended dose since side effects may occur which include increased nervousness, anxiety, irritability, difficulty in falling asleep, and occasionally disturbances in heart rate and rhythm called palpitations".

(2) "For occasional use only. If fatigue or drowsiness persists continuously for more than 2 weeks, consult a physician."

(3) "For adults only. Do not give to children under 12 years of age".

(4) For products containing caffeine: *"Contains caffeine.* Do not take this product with large amounts of caffeine-containing beverages such as coffee, tea or cola drinks".

Interested persons may, on or before March 8, 1976, submit to the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852, written comments (preferably in quintuplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal. Additional comments replying to any comments so filed may also be submitted on or before April 8, 1976. Received comments may be seen in the above office during working hours, Monday through Friday.

It is hereby certified that the economic and inflationary effects of this proposal have been carefully evaluated in accordance with Executive Order No. 11821.

Dated: December 1, 1975.

A. M. SCHMIDT,
*Commissioner of Food and Drugs.*

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