DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 336]

[Docket No. 78N-0036]

Antiemetic Drug Products for Over-the-Counter Human Use; Tentative Final Order

AGENCY: Food and Drug Administration.

ACTION: Tentative Final Order.

SUMMARY: This tentative final order would establish conditions under which over-the-counter (OTC) antiemetic drug products (products for the prevention and treatment of nausea and vomiting) are generally recognized as safe and effective and not misbranded. The agency is issuing this tentative final order after considering the report and recommendations of the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products, and public comments on the proposed rule that was based on those recommendations. This tentative final order is part of the Food and Drug Administration's ongoing review of OTC drug products.

DATE: Objections and/or requests for oral hearing before the Commissioner by August 13, 1979.

ADDRESS: Written objections and/or requests for oral hearing to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of March 21, 1975 (40 FR 12902), the Food and Drug Administration, under § 330.10(a)(6) (21 CFR 330.10(a)(6), published a proposed to establish monographs for over-the-counter (OTC) laxative, antidiarrheal, emetic, and antiemetic drug products, together with the recommendations of the OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Panel (Panel), which is the advisory review Panel responsible for evaluating data on drugs in these categories. Interested persons were invited to submit comments on the proposal within 90 days. For 30 days after the final day for submission of comments, reply comments could be filed with the Hearing Clerk in response to comments filed in the initial 90-day period.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, after deletion of a small amount of trade secret information.

In response to the proposal, 14 drug manufacturers and 1 consumer submitted 15 comments and reply comments. Having reviewed the comments and reply comments, the agency presents conclusions regarding OTC antiemetic active ingredients in this document.

The agency's conclusions on, and a tentative final order for, emetic active ingredients were published in the **Federal Register** of September 5, 1978 (43 FR 39544). The conclusions on, and tentative final monographs for, laxative and antidiarrheal active ingredients will be published in a later issue of the **Federal Register.**

The agency's conclusions regarding antiemetic active ingredients include a restatement of the Panel's recommendations and will constitute adoption of the Panel's findings, as modified on the basis of the comments and FDA's independent evaluation of the Panel's report. In addition to substantive modifications in the Panel's findings, the restatement will include changes for clarity and regulatory accuracy, and will also include any new data or information that has come to FDA's attention.

Based upon the above review and evaluation, the Food and Drug Administration concludes and advises:

1. That the conditions included in the monograph, under which OTC antiemetic drug products are generally recognized as safe and effective and not misbranded (Category I), will be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

2. That the conditions excluded from the monograph, under which OTC antiemetic drug products are not generally recognized as safe and effective or are misbranded (Category II), will be required to be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the **Federal Register,** regardless of whether further testing is undertaken to justify their future use.

3. That drug products with conditions excluded from the monograph because the available data are insufficient (Category III) to classify such conditions as either Category I or Category II will be permitted to remain on the market, or may be introduced into the market, after the date of publication of the final monograph in the **Federal Register,** provided that the FDA receives notification of testing in accordance with § 330.10(a)(13).

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call for data published in the **Federal Register** of February 8, 1973 (38 FR 3614). The OTC volumes and copies of comments and reply comments received are on public display in the office of the Hearing Clerk (address above).

I. The Commissioner's Conclusions on the Comments and Reply Comments

A. General Comments

1. One comment objected to the Panel's recommendation that the quantity of each active ingredient be stated in OTC drug product labeling, on the ground that section 502(e)(1)(A) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352(e)(1)(A)) provides for quantitative ingredient labeling only for prescription drug products.

The FDA responded to this objection in paragraph 1 of the preamble to the September 5, 1978 tentative final order for emetic active ingredients and reaffirms that conclusion.

2. Several comments objected to the Panel's recommendation that all inactive ingredients be listed on the labeling, arguing that such a listing would be meaningless to most consumers, confusing, and misleading.

The agency responded to these comments in paragraph 2 of the preamble to the September 5, 1978 tentative final order for emetic active ingredients and also reaffirms that response.

3. One comment stated that the proposed monographs, including the antiemetic drug monograph, violate the objectives and philosophy of the OTC drug review in that this Panel appeared to be intent on undermining the concept of self-medication with OTC laxatives, antidiarrheals, antiemetics, or emetics, and that the Panel failed to discharge its obligations.

The comment provides no basis for its allegations and the comment is rejected. The agency believes the Panel's recommendations and this tentative final monograph for OTC antiemetic drug products are fully in accord with the objectives of the OTC drug review to develop monographs based on the most

up-to-date scientific knowledge and data available.

4. Two comments contended that FDA does not have the authority to establish substantive rules.

This subject was dealt with in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products published in the **Federal Register** of May 11, 1972 (37 FR 9464), and the FDA reaffirms the conclusions stated there. Subsequent court decisions have confirmed the agency's authority to issue substantive regulations by rulemaking. See, e.g., *National Nutritional Foods Ass'n* v. *Weinberger*, 512 F. 2d 688, 696–98 (2d Cir. 1976).

5. Several comments urged a greater role for pharmacists in the sale of OTC drug products. One comment recommended that OTC drug products be available only through pharmacies, and two suggested that any labeling suggesting consultation with a physician should mention a pharmacist as a viable alternative.

These issues were fully discussed in the preamble to the proposal to revise requirements for drug interaction warnings on OTC drug products (see the **Federal Register** of June 4, 1974 (39 FR 19880)). These views will not be restated here. However, the agency notes that § 330.1(g) (21 CFR 330.1(g)) requires that labeling for OTC drugs include a warning to seek professional assistance in case of accidental overdose. The pharmacist is one of the health professionals that a consumer might choose to consult.

6. One comment noted that on several pages of the proposed monograph the abbreviation gm is used for gram, yet 21 CFR 201.62 (formerly 21 CFR 1.102d) states that the only abbreviation which may be used for gram is g.

Current regulations for all OTC drug monograph-related documents require the use of the abbreviation g for gram in accordance with the regulation cited in the comment. The situation outlined in the comment was an editorial oversight. Although the word "gram" or its abbreviation was not used in proposed Part 336 (21 CFR Part 336), other metric units of measure were abbreviated. To insure against inappropriate abbreviations, metric units have been fully written out in this tentative final order.

B. General Comments on Antiemetics

7. A comment requested that the indications for use of dimenhydrinate be revised to include "prevention" of motion sickness, making reference to the National Academy of Sciences/National Research Council (NAS/NRC) Drug Efficacy Study Group findings and the subsequent notice published by the agency in the **Federal Register** of June 4, 1971 (36 FR 10895).

The agency agrees that dimenhydrinate is generally recognized as safe and effective for prevention of the nausea and vomiting associated with motion sickness. The "prophylactic" use of dimenhydrinate was recommended by the NAS/NRC Drug Efficacy Study Implementation (DESI) review, and the agency has approved new drug applications (NDA's) for drug products with this indication in the product labeling. Because the term "prophylactic use" might not always be understood by the layman, the term "prevention" is used in OTC product labeling.

The agency also notes that the NAS/NRC recommended the prophylactic use of cyclizine hydrochloride and meclizine hydrochloride, and, therefore, concludes that labeling for these two antiemetic active ingredients may also contain a claim for the prevention as well as for the treatment of nausea and vomiting associated with motion sickness. Section 336.50 of the monograph is revised accordingly.

8. One comment requested reclassification of phosphorated carbohydrate (levulose-dextrose-ortho-phosphoric acid) from Category III to Category I and argued that the Panel did not adequately consider the submitted data, which included clinical studies, long usage, and patient acceptance of phosphorated carbohydrate as an OTC antiemetic of unquestioned safety.

The Panel thoroughly reviewed the material submitted to it on phosphorated carbohydrate and concluded that well-controlled, properly designed clinical studies are necessary to prove its effectiveness in the management of nausea and vomiting. The FDA concurs with the Panel's conclusions and rejects the comment.

9. Comments urged the agency to comment on scopolamine hydrobromide, pointing out that the Panel did not review this ingredient in spite of the availability of scopolamine hydrobromide products for motion sickness on the OTC market.

The Panel evaluated scopolamine hydrobromide as an antidiarrheal and concluded that there is insufficient evidence that it exerts an antidiarrheal effect. However, the Panel did not evaluate scopolamine hydrobromide as an antiemetic because no products containing it as an antiemetic were submitted.

During the comment period following publication of the March 21, 1975 proposal, data on a scopolamine hydrobromide drug product used as an OTC antiemetic were submitted to and evaluated by the agency (Refs. 1 through 16). These data consist of animal safety tests, testimony by authorities on the safety for OTC use of a 0.25 milligram (mg) dosage unit of scopolamine hydrobromide, and articles from the medical literature that purport to show that scopolamine hydrobromide in a single dosage of 0.6 to 1.0 mg is a safe and effective agent for the prevention and treatment of nausea and vomiting associated with motion sickness. These data are on file in the office of the Hearing Clerk, FDA. The literature indicates that, because of the increased incidence of unwanted side effects, the value of scopolamine hydrobromide diminishes if repetitive doses are necessary. The United States Pharmacopeia (U.S.P. XIX) (Ref. 17) lists the usual dose of scopolamine hydrobromide tablets as 0.6 to 1 mg as a single dose (as an anticholinergic agent). Goodman and Gilman's text (Ref. 18) lists the adult oral or parenteral dose of scopolamine hydrobromide as 0.6 mg and states that scopolamine in therapeutic doses normally causes drowsiness, euphoria, amnesia, fatigue, and dreamless sleep with a reduction in rapid-eye-movement (REM) sleep. The same doses occasionally cause excitement, restlessness, hallucinations, or delirium, especially in the presence of severe pain. The above dosage range is the one recommended for scopolamine hydrobromide as a prescription drug product.

The FDA is aware that, currently, there are OTC drug products on the market that are promoted for sleep and that contain 0.25 mg of scopolamine hydrobromide per unit dose as part of a combination of ingredients. The OTC Sedative, Sleep-Aid, and Tranquilizer Panel found (see **Fedeal Register** of December 8, 1975, at 40 FR 57302) and the agency concluded (see **Federal Register** of June 13, 1978, at 43 FR 25577) that scopolamine hydrobromide is not effective as a nighttime sleepaid in doses presently marketed, and that at higher, possibly more effective doses it would not be safe. There is evidence (Refs. 19 and 20) 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 oral doses of 0.6 mg and greater are dryness of the mouth, blurred vision, photophobia, and cardiac irregularities.

Occasionally, constipation, urinary retention, hypersensitivity reactions, actue glaucoma, excessive restlessness, and toxic psychosis can be seen. Infants, young children, and old people are especially susceptible to higher doses of the drug.

The scopolamine hydrobromide product submitted to FDA but not the Panel is for oral use as an OTC antiemetic for the prevention and treatment of nausea and vomiting associated with motion sickness and contains 0.25 mg scopolamine hydrobromide per unit dose. Labeling directions indicate that a dose can be repeated after 4 hours, but the total dose should not exceed 1.0 mg (4 doses per 24-hour period). The Panel chairman and a former FDA medical officer, serving as an agency consultant, agreed, and stated that they believed that Panel members would concur, that 0.25 mg is a safe dose for an OTC scopolamine hydrobromide drug product, provided it is used as the product labeling recommends, but that the existing data are insufficient to show that this proposed dose is an effective one. They, therefore, advised the agency that scopolamine hydrobromide should be classified as Category III to allow for effectiveness testing at this dosage level.

The FDA concludes that, although an OTC adult dosage of more than 0.25 mg of scopolamine hydrobromide to be taken every 4 to 6 hours would be unsafe, unit dosages of 0.25 mg (every 4 to 6 hours, not to exceed 1.0 mg in 24 hours) are safe for OTC use. However, having reviewed the literature submitted, the agency also concludes that the data are insufficient to show that the proposed dosage is effective for the prevention and treatment of nausea and vomiting associated with motion sickness. Thus, the FDA finds that well-controlled, double-blind clinical trials of scopolamine hydrobromide must be conducted to establish its effectiveness at this proposed dosage. Guidance for such studies is given elsewhere in this document. (See part II. paragraph D. below—Data Pertinent for Antiemetic Ingredient Evaluation.)

References

(1) Comment C–057, received in response to Proposed Establishment of Monograph for OTC Laxative, Antidiarrheal, Emetic and Antiemetic Products, published in the **Federal Register** of March 21, 1975 (40 FR 12902).

(2) "AMA Drug Evaluations—1973," 2d Ed., American Medical Association, Acton, p. 821, 1973.

(3) Brand, J. and W. Perry, "Drugs Used in Motion Sickness," *Physiological Reviews,* 13:895–924, 1964.

(4) DiPalma, J. R., "Drill's Pharmacology in Medicine," 4th Ed., McGraw-Hill, New York, pp. 609–620, 1974.

(5) Graybiel, A. and J. Knepton, "Direction-specific Adaptation Effects Acquired in a Slow Rotation Room," *Aerospace Medicine,* 43:1179–1189, 1972.

(6) Graybiel, A., D. Wood, E. Miller, and D. Cramer, "Diagnostic Criteria for Grading the Severity of Acute Motion Sickness," *Aerospace Medicine,* 39:453–455, 1968.

(7) Modell, W., "Drugs of Choice 1974–1975," C. V. Mosby Co., St. Louis, pp. 437–444, 1974.

(8) Money, K., "Motion Sickness," *Physiological Reviews,* 50:1–37, 1970.

(9) "The Pharmacopeia of the United States of America," 18th Rev., The United States Pharmacopeial Convention, Inc., Rockville, MD, p. 598, 1970.

(10) Tyler, D. and P. Bard, "Motion Sickness," *Physiological Reviews,* 29:311–369, 1949.

(11) Wood, D. and A. Graybiel, "A Theory of Motion Sickness Based on Pharmacological Reactions," *Clinical Pharmacology and Therapeutics,* 11:621–629, 1970.

(12) Wood, D. and A. Graybiel, "Theory of Antimotion Sickness Drug Mechanisms," *Aerospace Medicine,* 43:249–252, 1972.

(13) Wood, D. and A. Graybiel, and R. Kennedy, "Comparison of Effectiveness of Some Antimotion Sickness Drugs Using Recommended and Larger than Recommended Doses as Tested in the Slow Rotation Room," *Clinical Aviation and Aerospace Medicine,* 37:259–262, 1966.

(14) Wood, D. and A. Graybiel, and R. McDonough, "Human Centrifuge Studies on the Relative Effectiveness of Some Antimotion Sickness Drugs," *Clinical Aviation and Aerospace Medicine,* 37:187–190, 1966.

(15) Wood, D., R. Kennedy, and A. Graybiel, "Review of Antimotion Sickness Drugs from 1954–1964," *Aerospace Medicine,* 36:1–3, 1965.

(16) Wood, D., R. Kennedy, A. Graybiel, R. Trumbull, and R. Wherry, "Clinical Effectiveness of Anti-motion-Sickness Drugs," *Journal of the American Medical Association,* 198:133–136, 1966.

(17) "The Pharmacopeia of the United States of America," 19th Rev., 4th Supp., The United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 152–153, 1978.

(18) Innes, I. and M. Nickerson, "Atropine, Scopolamine, and Related Anti-miscarinic Drugs," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, pp. 517–523, 1975.

(19) Longo, V. G., "Behavioral and Electroencephalographic Effects of Atropine and Related Compounds," *Pharmacological Reviews,* 18:965–996, 1966.

(20) Eger, E. I., "Atropine, Scopolamine, and Related Compounds," *Anesthesiology,* 23:365–383, 1962.

10. A comment requested that the monograph be amended to include diphenhydramine hydrochloride as a Category I antiemetic. The comment stated that diphenhydramine hydrochloride has been available as a prescription drug for over 30 years, and that its effectiveness as a prescription antiemetic has been documented in the literature for most of that time. One diphenhydramine hydrochloride drug product available as a prescription product has had a claim for use as an antiemetic, based on both safety and effectiveness, since 1972. The comment further cites the NAS/NRC DESI review, which classified diphenhydramine hydrochloride as effective for motion sickness.

The comment stated that dimenhydrinate, one of the drugs reviewed by the Panel and placed in Category I, is actually a salt of diphenhydramine. Dimenhydrinate is the 8-chlorotheophylline salt of diphenhydramine, and, according to the comment, exists in solution as the independent ions, diphenhydramine and 8-chlorotheophylline. The comment contends that the antimotion sickness properties of dimenhydrinate actually derive from its diphenhydramine moiety. The comment stated that no data were submitted to the Panel because of the "confusion concerning dosages and indications that might result if oral preparations of diphenhydramine hydrochloride were being reviewed simultaneously by three OTC Panels."

The agency agrees that the effectiveness of diphenhydramine hydrochloride as an antiemetic for prescription use has been demonstrated in numerous studies, and recognizes that a supplemental NDA granted to a diphenhydramine hydrochloride product for use as an antiemetic was based on both safety and effectiveness data. The comment submitted no new data in support of its position that diphenhydramine hydrochloride is generally recognized as safe and effective for OTC use, however, other than a list of references documenting the effectiveness of diphenhydramine hydrochloride in motion sickness.

As recognized by the comment, this Panel did not review any data on the use of diphenhydramine hydrochloride as an antiemetic because none were submitted. Under the OTC Drug Review procedures, if a drug product is claimed to be effective for more than one indication, the safety and efficacy data for each indication must be submitted to, and reviewed by, the OTC drug review panel responsible for that indication. The comment does not explain why simultaneous review of this ingredient by three OTC panels might result in confusion concerning dosages and indications. The two OTC advisory

review panels that reviewed diphenhydramine hydrochloride were the Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products Panel, which reviewed it as an antihistamine and antitussive, and the Sedative/Sleep-Aid Drug Products Panel, which reviewed it as a nighttime sleep-aid. The Sedative/Sleep-Aid Panel classified diphenhydramine hydrochloride in Category III as an OTC nighttime sleep-aid, thus recognizing as a benefit the drownsiness which the drug produces. Under § 330.13 (21 CFR 330.13), OTC marketing of diphenhydramine hydrochloride as a nighttime sleep-aid cannot occur until the required Category III testing has been completed and the agency determines that the data support a finding that diphenhydramine hydrochloride is generally recognized as safe and effective for such use.

The Cold/Cough Panel recommended that diphenhydramine hydrochloride be classified in Category I for use both as an OTC antihistamine and as an OTC antitussive. In the preamble to the Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products Panel report (see **Federal Register** of September 9, 1976, at 41 FR 38313) the agency disagreed with these recommendations, stating that diphenhydramine hydrochloride has a pronounced tendency to produce sedation in a high proportion of those persons who take it, and for this reason, it should remain a prescription new drug ingredient and not be available for use as an OTC antihistamine. The use of diphenhydramine hydrochloride as an OTC antitussive was discussed in the **Federal Register** of November 30, 1976 (41 FR 52536). In that notice, the FDA concluded that the incidence of drowsiness (⅛ of the study population reported the occurrence of drowsiness) associated with the use of diphenhydramine hydrochloride as an antitussive made its use as an OTC antitussive unacceptable for reasons of safety, even with the proposed warning statement contained in the labeling recommended by the Cold/Cough Panel.

In weighing the significance of the drowsiness caused by diphenhydramine hydrochloride, consideration must be given to the conditions of use for which it is intended. If used as an OTC antiemetic, diphenhydramine hydrochloride would be indicated for use only in the prevention and treatment of nausea and vomiting associated with motion sickness. For persons afflicted with motion sickness while traveling aboard ship, in airplanes, or in automobiles, as opposed to persons driving or piloting these vehicles, drowsiness might not present a safety problem, nor is it necessarily an unpleasant or unwelcome side effect. However, neither diphenhydramine hydrochloride nor any other OTC antiemetic should be used by anyone who is operating a motor vehicle or other machinery or equipment, and the labeling for all OTC antiemetic drug products requires a warning to this effect. (See Subpart D, § 336.50(c)(1) below.)

Having reviewed all of the data submitted, the FDA concludes that diphenhydramine hydrochloride should be placed in Category III at this time for use as an OTC antiemetic agent based on its apparent chemical and pharmacological similarity to dimenhydrinate, which the Panel has classified as Category I. Dimenhydrinate contains 53.0 to 55.5 percent diphenhydramine and 44.0 to 47.0 percent 8-chloro-theophylline (Ref. 1). The role of the 8-chlorotheophylline in dimenhydrinate is unknown. The substance 8-chlorotheophylline is a xanthine derivative with central nervous system (CNS) stimulant properties similar to caffeine; it may have some role in counteracting the sedative effect of the diphenhydramine in dimenhydrinate.

The agency believes, however, that clinical evidence is needed to establish that diphenhydramine hydrochloride is comparable in safety to dimenhydrinate for OTC antiemetic use. The agency proposes that clinical studies be conducted which compare diphenhydramine hydrochloride to dimenhydrinate and a placebo for the depth and length of drowsiness. Such studies should also include blood level determinations to evaluate a possible blood level correlation of the active diphenhydramine moiety with the extent of drowsiness and the CNS effect that the 8-chlorotheophylline exerts. Adequate blood samples should be taken to determine the maximum blood level concentrations for each drug. The same subjects could be used in crossover studies on diphenhydramine hydrochloride and dimenhydrinate under comparable dosing schedules (25 to 50 mg diphenhydramine hydrochloride compared to 50 to 100 mg dimenhydrinate). These studies may adequately establish or disprove the similarity of action between both forms of diphenhydramine without more lengthy clinical trails being needed. If the sedative effects of diphenhydramine hydrochloride are shown not to be significantly different from those of dimenhydrinate, then diphenhydramine hydrochloride can be generally recognized as safe and effective (Category I) as an OTC antiemetic drug product.

Under § 330.13, marketing of diphenhydramine hydrochloride as an OTC antiemetic cannot begin until the required testing has been completed pursuant to the Category III Testing Guidelines (see the **Federal Register** of April 12, 1977 (42 FR 19137)) and the agency has reviewed the results of the studies and determines that diphenhydramine hydrochloride is generally recognized as safe and effective for OTC use as an antiemetic drug product.

Reference

(1) "The Pharmacopeia of the United States of America," 19th Rev., The United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 151–152, 1975.

11. A comment noted the Panel's statement that studies evaluating the effectiveness of bismuth compounds for "upset stomach" or "nausea" suffer from the vague definitions of these complaints. The comment suggested that upper G.I. discomfort, or upset stomach, be defined as a distressing condition of the abdomen (usually upper abdomen) which symptomatically may include nausea, indigestion, slight to moderate pain, a feeling of fullness, distention, or pressure. Its usual causes are overindulgence in food or ingestion of spices, alcohol, tobacco, or certain drugs.

The agency advises that the use of bismuth compounds in treating "upset stomach" as defined by the comment has been referred to the Advisory Review Panel on OTC Miscellaneous Internal Drug Products. The use of bismuth compounds in treating "nausea" associated with motion sickness or other conditions is discussed elsewhere in this document. (See part II. paragraph B.3.a.—Bismuth subsalicylate.)

12. Several comments argued that the 2-year study period recommended by the Panel for Category III active ingredients and combination products is inadequate to develop and perform the testing necessary to establish the effectiveness of these ingredients.

The Panel gave careful consideration to the question of a reasonable time period for conducting the testing to which the comments refer. The Panel concluded that a period of 2 years is adequate to develop and perform this testing. The agency agrees with the Panel's decision and rejects the comments.

II. The Commissioner's Conclusions on Antiemetics

A. General Discussion

Severe nausea and the realization that one is about to vomit are among the more uncomfortable conditions suffered by people. Motion sickness occurs when visual and vestibular (sense of balance) stimuli are not in accord, particularly when the head rotates in two axes simultaneously. Motion sickness accompanied by nausea and/or vomiting is not an unusual occurrence. Some individuals are more resistant to motion sickness than others, but apparently no one is immune. Travel aboard ship, in airplanes, or even in automobiles may induce motion sickness. Motion sickness may be effectively prevented and treated by a number of antihistamine-like drugs available in OTC antiemetic drug products. Protection against motion sickness is best accomplished by taking the antiemetic drug product ½ to 1 hour before travelling.

OTC antiemetics may also be used in the treatment of nausea and vomiting other than that associated with motion sickness. The Panel noted that the claims for effectiveness for the treatment of nausea and vomiting due to these other causes have not been proven and that such claims for an ingredient must be proven in well-controlled clinical studies. The FDA concurs and, accordingly, the only indication for OTC antiemetics established at this time is the claim "for the prevention and treatment of nausea and vomiting associated with motion sickness."

B. Safety and Effectiveness

The agency has reviewed all claimed active ingredients submitted to the Panel as well as other available data and information in arriving at these conclusions and recommendations.

For the convenience of the reader, the following table summarizes the conclusions regarding categorization of single antiemetic active ingredients:

Categorization of Antiemetic Single Active Ingredients

Active ingredient	Antiemetic category
Aminoacetic acid	II
Bismuth subsalicylate	III
Cyclizine hydrochloride	I
Dimenhydrinate	I
Diphenydramine hydrochloride	III
Meclizine hydrochloride	I
Phenyl salicylate	II
Phosphorated carbohydrate	III
Scopolamine hydrobromide	III
Zinc phenolsulfonate	II

The agency notes that the Panel was unable to find any evidence to support claims that phenyl salicylate and zinc phenolsulfonate, alone or in combination, are effective as antiemetic or antinauseant drugs. The agency is also unable to find any evidence of effectiveness of these ingredients and, therefore, reclassifies them from Category III, as recommended by the Panel, to Category II.

1. *Conditions under which antiemetic drug products are generally recognized as safe and effective and are not misbranded.* The following antiemetic active ingredients are classified as safe and effective and not misbranded:

Benzhydryl piperazine antihistamines
- Cyclizine hydrochloride
- Meclizine hydrochloride

Dimenhydrinate

a. *Benzhydryl piperazine antihistamines (cyclizine hydrochloride and meclizine hydrochloride).* The FDA concludes that cyclizine hydrochloride and meclizine hydrochloride are safe and effective in the amounts taken orally (meclizine hydrochloride, for adults 25 to 50 mg once daily; and cyclizine hydrochloride, for adults 50 mg every 4 to 6 hours, not to exceed 200 mg in 24 hours, and for children 6 years of age and older, 25 mg every 6 to 8 hours, not to exceed 75 mg in 24 hours) in OTC antiemetic drug products for the prevention and treatment of nausea and vomiting associated with motion sickness.

Meclizine hydrochloride and cyclizine hydrochloride are members of the benzhydryl piperazine group of antihistamine compounds. Chemically, these compounds differ from other antihistamines in that the alkylamino group exists as a ring structure.

Many studies reported in the medical literature support the conclusion that meclizine hydrochloride is safe and effective in the management of motion sickness (Refs. 1 through 5). The drug has a relatively long duration of action and is reported to afford 24-hour protection against the symptoms of motion sickness (Refs. 3 and 4).

Meclizine hydrochloride is relatively free of side effects when administered in therapeutic doses, although drowsiness sometimes occurs and may be troublesome to those persons who drive automobiles or operate other machinery. Packages of OTC meclizine hydrochloride tablets are currently required by § 310.201(a)(6) (21 CFR 310.210(a)(6)) to contain warnings of this potential hazard. Section 336.50(c)(1) of the antiemetic drug products monograph will likewise require warnings of this potential hazard.

In 1966, FDA, acting on the recommendation of an Ad Hoc Advisory Committee on the Teratogenic Effect of Certain Drugs, required relabeling, through NDA supplements, of drug products containing meclizine hydrochloride and cyclizine hydrochloride to include the following warning: "Warning—Not for use by women who are pregnant or who may possibly become pregnant, unless directed by a physician, since this drug may have the potentiality of injuring the unborn child." This labeling warning was prompted by concern that the drugs may have teratogenic or embryolethal potential. The Panel carefully reviewed the report of the FDA Ad Hoc Advisory Committee in light of more recent epidemiological data, and the position of the American Teratology Society regarding the limitations of extrapolating animal data to man (Ref. 6). Epidemiological data on 50,282 pregnant women, 1,014 of whom had used meclizine hydrochloride during the early stages of pregnancy, indicate that the incidence of malformation of the offspring of the 1,014 women was not statistically greater than that of the control group (who had taken other drugs during pregnancy). Further, there is indirect evidence that meclizine hydrochloride is not toxic to the embryo and that the incidence of specific teratogenicity e.g., cleft palate, was lower in the human pregnancy data than might have been expected from the animal studies that led to the pregnancy warning (Ref. 7). The Panel concluded, and the agency concurs, that the data do not support a restriction in the use of meclizine hydrochloride or cyclizine hydrochloride or a pregnancy warning. Thus, the existing regulations in § 201.307 (21 CFR 201.307) and § 310.201(a)(6) specifying warnings for meclizine hydrochloride and cyclizine hydrochloride drug products will be superseded and withdrawn at the time this monograph becomes effective. This decision applies both to OTC products and to products currently available by prescription only.

An OTC claim for the effectiveness of the benzhydryl piperazine antihistamines is permissible only for the prevention and treatment of nausea and vomiting associated with motion sickness. Claims for the prevention and treatment of nausea and vomiting from other causes have not been proven. The labeling must carry the warning that drowsiness sometimes results from taking the product and caution persons (1) not to operate motor vehicles or

other machinery or equipment while taking it and (2) to avoid alcoholic beverages while taking it (because of the additive central nervous system depressant effects that may occur). Patients must also be warned not to take cyclizine hydrochloride and meclizine hydrochloride if they have asthma, glaucoma, or enlargement of the prostate gland except under the advice and supervision of a physician. The agency advises that it has added "asthma" to the Panel's recommended warning because of the anticholinergic action of these drugs. In patients with asthma, antihistamines may cause drying of bronchial secretions, making expectoration of the secretions more difficult and thereby increasing obstruction of the airway.

The labeling must also contain a warning against administration to children under 6 years of age (cyclizine hydrochloride) or 12 years of age (meclizine hydrochloride) except under the advice and supervision of a physician.

On June 27 and 28, 1977, FDA's Neurologic Drugs Advisory Committee concluded that meclizine hydrochloride is safe and effective for the treatment of vertigo (Ref. 8). The FDA concurs in that decision. However, vertigo is not amenable to self-diagnosis and treatment by the layman, but must be left to the professional diagnosis and treatment of a physician. Accordingly, the claim for vertigo is not permitted on OTC antiemetic drug product labeling but may appear in professional information for the physician, and the monograph is amended to include professional labeling for meclizine hydrochloride.

References

(1) Chinn, H. I., et al., "Evaluation of Drugs for Protection Against Motion Sickness Aboard Transport Ships," *Journal of the American Medical Association*, 160:755–760, 1956.

(2) Arner, O., H. Diamant, L. Goldberg, and G. Wrange, "Antihistamines in Sea Sickness," *Archives Internationales de harmacodynamie et de Therapie*, 117:404–418, 1958.

(3) Handford, S. W., T. E. Cone, H. I. Chinn, and P. K. Smith, "Drugs Preventing Motion Sickness at Sea," *Journal of Pharmacology and Experimental Therapeutics*, 11:447–453, 1954.

(4) Chinn, H. I., S. W. Handford, P. K. Smith, T. E. Cone, R. F. Redmond, J. V. Maloney, and C. M. Smythe, "Evaluation of Some Drugs in Seasickness," *Journal of Pharmacology and Experimental Therapeutics, 108:69–79, 1953.*

(5) Franks, J. J., L. J. Milch, and E. V. Dahl, "Prevention of Airsickness with Meprobamate," *Journal of the American Medical Association*, 181:263–264, 1962.

(6) Staples, R. E., "Teratogens and the Delaney Clause," *Science*, 185:813–814, 1974.

(7) Shapiro, S., Boston Children's Medical Center, Testimony Before OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Panel, October 11, 1974.

(8) Minutes of the Seventh Meeting of the Neurologic Drugs Advisory Committee, Bureau of Drugs, Food and Drug Administration, June 27–28, 1977, pp. 14–16.

b. *Dimenhydrinate.* The FDA concludes that dimenhydrinate is safe and effective in the amounts taken orally in OTC antiemetic products for the prevention and treatment of nausea and vomiting associated with motion sickness. The dosage for adults is 50 to 100 mg every 4 to 6 hours, not to exceed 400 mg in 24 hours. The dosage for children 2 to under 6 years of age is 12.5 to 25 mg every 6 to 8 hours, not to exceed 75 mg in 24 hours, and for children 6 to under 12 years of age is 25 to 50 mg every 6 to 8 hours, not to exceed 150 mg in 24 hours.

Dimenhydrinate is the 8-chlorotheophylline salt of the antihistamine diphenhydramine. Since the introduction of dimenhydrinate in 1949, its effectiveness against seasickness and airsickness has been repeatedly demonstrated. Dimenhydrinate is relatively free of side effects when administered in recommended doses, although drowsiness sometimes occurs and may prove troublesome to individuals operating a motor vehicle or other types of machinery or equipment (Refs. 1 and 2).

The only OTC claim that may be made for dimenhydrinate is "for the prevention and treatment of nausea and vomiting associated with motion sickness." The agency is unaware of the existence of acceptable scientific data to support a claim for effectiveness in the treatment of nausea and vomiting from other causes.

The labeling for dimenhydrinate must carry the warning that drowsiness sometimes results from taking the product and caution persons (1) not to operate motor vehicles or other machinery or equipment while taking it and (2) to avoid alcoholic beverages while taking it (because of the additive central nervous system depressant effects which may occur). Patients must also be warned not to take dimenhydrinate if they have asthma, glaucoma, or enlargement of the prostate gland except under the advice and supervision of a physician.

In the **Federal Register** of July 29, 1977 (42 FR 38645), FDA published a DESI followup notice and opportunity for hearing, setting forth the conditions for marketing prescription drug products of dimenhydrinate for the indication for which they continue to be regarded as effective. This notice applied to dimenhydrinate drug products in suppository or sterile solution form suitable for rectal or parenteral administration respectively, "For the prevention and treatment of the nausea, vomiting, or vertigo of motion sickness."

The DESI notice advised that dimenhydrinate tablets and liquid were being handled by the OTC review. As the OTC claim for dimenhydrinate is "for the prevention and treatment of nausea and vomiting associated with motion sickness" and the prescription dosage forms may also be labeled "for the vertigo of motion sickness," the agency concludes that the claim of "for the treatment of vertigo of motion sickness" may appear in professional information for the physician. The monograph is amended to include such professional labeling for dimenhydrinate.

References

(1) Gay, L. N. and P. E. Carliner, "The Prevention and Treatment of Motion Sickness. I. Seasickness," *Science*, 109:359, 1949.

(2) Chinn, H. I. and P. K. Smith, "Motion Sickness," *Pharmacological Reviews*, 7:33–82, 1955.

2. *Conditions under which antiemetic drug products are not generally recognized as safe and effective or are misbranded.* There is no scientific basis for the claims of effectiveness of a number of ingredients used in OTC antiemetic drug products. Based on this finding, the FDA concludes that the following ingredients should be removed from the market as antiemetic agents regardless of whether further testing is undertaken to justify their future use:

Aminoacetic acid (glycine, glycocol)
Phenyl salicylate (salol)
Zinc phenolsulfonate

a. *Aminoacetic acid (glycine, glycocol).* The FDA concludes that aminoacetic acid is safe in the amounts usually taken orally in OTC drug products, but that there is no evidence to support its effectiveness as an antiemetic agent.

Glycine is classified as a Category I active ingredient in the OTC Antacid Monograph (21 CFR 331.11(f)). However, because hyperacidity is not a known cause of vomiting, there is no sound theoretical or scientific basis to suggest that the addition of glycine to antiemetic drug products would offer relief of nausea and vomiting. The agency can

find no evidence to support the claim that glycine, alone or in combination, is an effective antiemetic or antinauseant.

b. *Phenyl salicylate (salol).* The FDA concludes that phenyl salicylate is safe in the amounts usually taken orally in OTC products, but can find no evidence to support its effectiveness as an antiemetic agent.

c. *Zinc phenolsulfonate.* The FDA concludes that zinc phenolsulfonate is safe in amounts usually taken orally in OTC products, but can find no evidence to support its effectiveness as an antiemetic agent.

3. *Conditions for which the available data are insufficient to permit final classification at this time.* The FDA concludes that adequate and reliable scientific evidence is not available at this time to permit final classification of the active ingredients listed below:

Bismuth subsalicylate
Diphenhydramine hydrochloride
Phosphorated carbohydrate (levulose-dextrose-ortho-phosphoric acid)
Scopolamine hydrobromide

The agency believes it reasonable to allow 2 years for the development of such evidence. Marketing need not cease during this time for these active ingredients currently being marketed as OTC antiemetics products if adequate testing is undertaken in accordance with § 330.10(a)(13). If adequate effectiveness and/or safety data are not obtained and submitted to the agency within 2 years, however, the ingredients listed in this category may no longer be marketed as active ingredients in OTC antiemetic drug products. Under 21 CFR 330.13, OTC CFR 330.13, OTC marketing of diphenhydramine hydrochloride as an antiemetic cannot commence until the required Category III testing has been completed and the agency determines that the data support a finding that diphenhydramine hydrochloride is generally recognized as safe and effective for such use. (See part I, paragraph B.10. above and 21 CFR 330.13.)

The agency has carefully considered the types of studies required for removing a claimed active antiemetic ingredient from Category III and placing it in Category I. (See part II. paragraph D. below—Data Pertinent for Antiemetic Ingredient Evaluation.) In general, to demonstrate effectiveness, the design of the study should have a sound scientific basis, e.g., a randomized, double-blind, crossover study comparing the claimed active ingredient to placebo. The clinical trial should be carefully controlled, e.g., consideration should be given to selection of subjects representative of the general population as well as to the diet, activity, travel, etc., of subjects being studied. Quantitative measurement of various parameters is appropriate for the claimed effects of the ingredient.

a. *Bismuth subsalicylate.* The FDA concludes that bismuth subsalicylate is safe in the amounts usually taken (up to 4.8 g daily) orally, but that there is insufficient evidence to establish its effectiveness as an antinauseant/antiemetic.

The agency is aware of recent published reports from France and Australia (Refs. 1 through 5) of reversible myoclonic encephalopathies occurring in patients ingesting certain bismuth salts, especially bismuth subnitrate and bismuth subgallate. The precise cause of these reactions, which have not been previously reported with bismuth use, is uncertain. Epidemiological findings suggest possible transformation of bismuth to a toxic form by certain bacteria in the bowel of affected individuals. Because of the restricted geographical distribution of the reactions, i.e., to France and Australia, no action seems indicated against bismuth-containing drug products marketed in the United States at this time.

Evidence available to the agency indicates that emesis in dogs induced by 15 milliliters (mL) of ipecac syrup can be controlled effectively by pretreatment with 0.35 g/kg of bismuth subsalicylate in a liquid preparation (Ref. 6). In human subjects, 1 ounce (oz) of a bismuth preparation was no more effective than 1 oz of water in preventing emesis which had been induced by a dose of 15 mL of ipecac syrup.

Bismuth compounds appear to control the uncomfortable feelings accompanying low doses of ipecac syrup, but it is difficult to study the effect of any drug on distention symptoms induced by overeating unless the drug affects gastric emptying time, the tone of the stomach wall, or intragastric pressure.

The Panel noted that bismuth subsalicylate is not promoted as an antimotion sickness active ingredient. If it is desired to test bismuth subsalicylate as an agent to reduce or control nausea and vomting due to motion sickness, the testing should be performed according to the effectiveness standards set forth below. Evaluation of the effectiveness of bismuth subsalicylate in reducing or controlling nausea and vomiting due to causes other than motion sickness requires well-controlled clinical trials in uniform groups of subjects with nausea and vomiting associated with specific conditions. (See part II. paragraph D. below—Data Pertinent for Antiemetic Ingredient Evaluation.)

References

(1) Meyboom, R. H. B., "Metals" *in* "Meyler's Side Effects of Drugs," Volume 8, Edited by Meyler, L. and A. Herxheimer, p. 503, 1975.

(2) Robertson, J. F., "Mental Illness or Mental Illness? Bismuth subgallate," *The Medical Journal of Australia,* 1:887–888, 1974.

(3) Morgan, F. P. and J. J. Billings, "Is This Subgallate Poisoning?," *The Medical Journal of Australia,* 2:662–663, 1974.

(4) Buge, A. et al., "Twenty Cases of Acute Encephalophathy with Myoclonia During Treatment with Oral Bismuth Salts," *Annales de Medicine Interne,* 125:877–888, 1974.

(5) Martin-Bouyer, "Intoxications par les Sels de Bismuth Administres par Voie Orale," *Gastroenterologie Clinique et Biologique,* 2:349–356, 1978.

(6) OTC Volune 090123.

b. *Diphenhydramine hydrochloride.* The FDA concludes that diphenhydramine hydrochloride is safe in the amounts taken orally as a prescription medication for antiemetic use. The prescription dosage for adults is 25 to 50 mg every 4 to 6 hours, and for children 6 to under 12 years of age, 12.5 to 25 mg every 4 to 6 hours, not to exceed 300 mg in 24 hours. The prescription dosage for children 2 to under 6 years of age is 6.25 to 12.5 mg every 4 to 6 hours. However, clinical evidence is needed to establish that diphenhydramine hydrochloride is comparable in safety to dimenhydrinate for OTC antiemetic use. Dimenhydrinate, which the Panel classified as a Category I antiemetic agent, is the 8-chlorotheophylline salt of diphenhydramine. Dimenhydrinate contains 53.0 to 55.5 percent diphenhydramine and 44.0 to 47.0 percent 8-chlorotheophylline (Ref. 1.).

The agency proposes that clinical studies be conducted which compare diphenhydramine hydrochloride to dimenhydrinate and to a placebo for the depth and length of drownsiness. Such studies should also include blood level determinations to evaluate a possible blood level correlation of the active diphenhydramine moiety with the extent of drowsiness and the CNS effect that the 8-chlorotheophylline exerts. The same exerts. The same subjects could be used in crossover studies on diphenhydramine hydrochloride and dimenhydrinate to determine the amount and levels of diphenhydramine which reach the bloodstream from both drugs under comparable dosing schedules. (See part I. paragraph B.10. above.)

The effectiveness of diphenhydramine hydrochloride as an antiemetic at its established dosage is not at issue; that indication has been approved for prescription usage through the new drug procedures. In addition, NAS/NRC, as part of the DESI review, classified diphenhydramine hydrochloride as effective for the prevention and treatment of motion sickness.

Reference

(1) "The Pharmacopeia of the United States of America," 19th Rev., The United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 151–152, 1975.

c. *Phosphorated carbohydrate (levulose-dextrose-orthophosphoric acid).* Phosphorated carbohydrate preparations consist of a solution containing invert sugar (a mixture of equimolar amounts of levulose and dextrose obtained by hydrolysis of sucrose) and phosphoric acid which is used to adjust the pH of the solution to a range of 1.5 to 1.6. The FDA concludes that phosphorated carbohydrate is safe in the amounts usually taken orally as a single dose, i.e., 1 or 2 tablespoons (15 to 30 mL), which contain approximately 8 to 18 g of invert sugar.

However, the manufacturer's recommended dosage for this solution for adults is 1 or 2 tablespoons every 15 minutes until distress subsides, with the caution that the solution is not to be taken for more than 1 hour (5 doses) without consulting a physician. Thus, it is possible that an adult could take up to 10 tablespoonfuls of the solution, or 85 to 90 g of invert sugar, in a 1-hour period. Invert sugar contains about 50 percent glucose (dextrose) and 50 percent fructose (levulose) obtained by the hydrolysis of sucrose (Ref. 1). Ingestion of this much invert sugar during a 1-hour interval represents a potential problem for diabetics (Ref. 2). The agency will, therefore, require that this solution bear the following warning, which should be conspicuously boxed and in red letters: "This product contains sugar and should not be taken by diabetics except under the advice and supervision of a physician." In addition, because the product contains levulose (fructose), the solution must bear the warning: "This product contains fructose and should not be taken by persons with hereditary fructose intolerance (HFI)."

A mixture of carbohydrate (invert sugar) and phosphoric acid has the potential to inhibit gastric emptying as a consequence of the inhibition of gastric peristalsis and a reduction in gastric tone. It has been reported that the high osmotic pressure exerted by concentrated solutions of simple sugars (monosaccharides) inhibits gastric emptying through an action on duodenal osmoreceptors which are sensitive to high osmotic pressures (Ref. 3). This potential mechanism of action has been cited in support of the effectiveness of phosphorated carbohydrate in treating nausea and vomiting. However, a positive correlation between an increase in gastric emptying time and the relief of nausea and vomiting has not been established.

Only a few clinical studies have been reported on the use of a carbohydrate-phosphoric acid preparation for the management of nausea and vomiting. Most of these were either uncontrolled or partially controlled investigations (Refs. 4 through 6). The only double-blind clinical investigation reported was poorly designed (Ref. 7).

The FDA concludes that there is insufficient evidence to establish the effectiveness of phosphorated carbohydrate solution as an antinauseant/antiemetic agent and that well-controlled, properly designed clinical studies are needed to establish its effectiveness for the control of nausea or vomiting. (See part II. paragraph D. below—Data Pertinent for Antiemetic Ingredient Evaluation.)

Current labeling for phosphorated carbohydrate solution includes claims that the product is effective for the relief of nausea and vomiting associated with colds, intestinal "flu," grippe, "food indiscretions," motion sickness, travel discomfort, and emotional upsets. There is also a labeling claim for the control of vomiting and regurgitation in infants. The agency concurs with the Panel that there is insufficient evidence to establish the effectiveness of phosphorated carbohydrate solution as an antinauseant/antiemetic agent for each of these indications. Accordingly these claims are classified in Category III, and it will be necessary for firms to test the drug for each of its intended claims during the Category III testing period.

References

(1) "The Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, p. 4863, 1976.

(2) Cerasi, C., S. Efendic, and R. Luft, "Dose-Response Relation Between Plasma-Insulin and Blood-Glucose Levels During Oral Glucose Loads in Prediabetic and Diabetic Subjects," *Lancet,* 1:794–797, 1973.

(3) Van Liere, E. J., D. W. Northrup, and J. C. Stickney, "The Effect of Glucose on the Mobility of the Stomach and Small Intestine," *Gastroenterology,* 7:218–223, 1946.

(4) Bradley, J. E., L. Proutt, E. R. Shipley, and R. H. Oster, "An Evaluation of Carbohydrate-Phosphoric Acid Solution in the Management of Vomiting," *Journal of Pediatrics,* 38:41–44, 1951.

(5) Crunden, A. B., Jr. and W. A. Davis, "The Oral Use of a Phosphorated Carbohydrate Solution in Nausea and Vomiting of Pregnancy," *American Journal of Obstetrics and Gynecology,* 65:311–313, 1953.

(6) Tebrock, H. E. and M. M. Fisher, "Nausea and Vomiting: Evaluation of an Orally Administered Phosphorated Carbohydrate Solution," *Medical Times,* 82:271–275, 1954.

(7) Agerty, H. A., "A Phosphorated Carbohydrate Solution for the Prevention of Motion Sickness," *Adult and Child,* 1:66, 1969.

d. *Scopolamine hydrobromide.* The FDA concludes that scopolamine hydrobromide is safe (in an adult oral dosage of 0.25 mg every 4 to 6 hours, not to exceed 1.0 mg in 24 hours) but additional data are needed to show its effectiveness as an antiemetic agent at this dosage. This conclusion is based on the agency's evaluation of data on a scopolamine hydrobromide drug product used as an OTC antiemetic submitted subsequent to the Panel's final meeting. (See part I. paragraph B.9. above.)

The scopolamine hydrobromide product on which data were submitted is promoted to protect against car sickness, sea sickness, plane sickness, and train sickness. The product bears claims that it is "scientifically developed to help your 'Balance Control Center' stay level, while decreasing your sensitivity to imbalance * * * helps prevent dizziness, stomach upset, nausea." Based on the data reviewed, there is insufficient evidence to establish that scopolamine hydrobromide at the above dosage is effective for the prevention and treatment of nausea and vomiting associated with motion sickness. Moreover, if the sponsor intends to promote the product for any indication, i.e., dizziness, stomach upset, or to make any claim apart from the general claims for the prevention and treatment of nausea and vomiting associated with motion sickness, the product must be tested for each of these specific claims, as specified below.

Well-controlled, double-blind clinical trials are needed to compare the antiemetic effect of scopolamine hydrobromide, at the above dosage, alone or in combination, with a placebo. Careful experimental design, definition of terms, and matching of subjects is needed to assess the effect on subjective complaints of nausea and objective changes in the frequency of vomiting. (See part II. paragraph D. below—Data Pertinent for Antiemetic Ingredient Evaluation.)

C. Drug Products Containing Multiple Antiemetic Ingredients

The Panel did not classify any OTC antiemetic combination drug products as Category I or III. The Panel concluded that, in general, the fewer the ingredients in a drug product, the safer and more rational the therapy. The agency agrees that OTC antiemetic drug products should be single active ingredient products. The agency also believes that it would be unsafe to combine two Category I antihistamine-type antiemetics at therapeutic concentrations because of the additional drowsiness and anticholinergic effects that would result. Thus, because current Category I antiemetic active ingredients are also antihistamines, there are no Category I combination antiemetic drug products.

The Panel reviewed antiemetic combination drug products containing two or more nonantihistamine antiemetic active ingredients. Except for the bismuth subsalicylate contained in these products, all of the other active ingredients have been placed in Category II. The agency is unaware of any other drug products containing multiple antiemetic active ingredients and concludes that any OTC combination drug product containing two antiemetic active ingredients is classified as Category II. Likewise, the agency is unaware of any combination drug product containing an antiemetic active ingredient, labeled for use as an antiemetic, in combination with any other active ingredient from a different therapeutic group. These combinations are also classified as Category II.

D. Data Pertinent for Antiemetic Ingredient Evaluation

In its report, the Panel recommeded that certain toxicology and metabolism data be obtained to demonstrate the safety of antiemetic drug products. The metabolism studies were to focus on the absorption, distribution, fate, and excretion (ADFE) of the drug. Safety is not at issue in the Category III testing of OTC antiemetic drug products, except for diphenhydramine hydrochloride. (See part I. paragraph B.10. above.) Accordingly, these testing requirements have been deleted in this document.

The agency recognizes the lack of physiological data on the gastorintestinal receptors and effectors of emesis and the related difficulty in establishing the mechanism of action of agents acting on either the central or autonomic nervous system or directly affecting gastric motility or tone. However, certain data should be provided which serve to elucidate the pharmacologic effects of antiemetic agents. Manufacturers are expected to obtain only those data relevant to the unanswered questions regarding the pharmacologic effects of their products:

a. Effects of oral drug on nausea and vomiting.

b. Effects of oral drug on cardiovascular system (blood pressure and heart rate).

c. Effects of oral drug on autonomic nervous system.

d. Duration of oral drug effects.

e. Effects on drowsiness and the central nervous system.

1. *Effectiveness standards.* Motion sickness, which may occur when visual and vestibular stimuli are not in accord, may be induced by a number of techniques. Unusual motion patterns in which the head is rotated in two axes simultaneously will produce motion sickness in anyone; some individuals are more resistant than others, but apparently no one is immune. Motion sickness may also be induced when the body is stationary and the individual looks at a motion picture film such as the view from an airplane doing acrobatics or from a roller coaster ride (Ref. 1). Thus, a number of experimental models are available to test the effectiveness of antiemetic agents intended for the prevention and treatment of nausea and vomiting associated with motion sickness. Both normal individuals and subjects with known susceptibility to motion sickness should be tested. The threshold of stimulus (duration in time, rotation rate in revolutions per minute, and acceleration rate) to induce motion sickness should be determined before and after the test drug is administered to determine degree of effectiveness and duration of time of protection from motion sickness. The degree of drowsiness caused by the drug should also be determined. Comparisons should be made with a placebo using a double-blind technique. Manufacturers need to obtain only those data relevant to the unanswered questions regarding the effectiveness of their products.

Determination of the effectiveness of an antiemetic active ingredient in reducing or controlling nausea and vomiting due to causes other than motion sickness requires well-controlled clinical trials in uniform groups of subjects with nausea and vomiting associated with specific conditions.

2. *Requirements for specific Category III active ingredients.* There are four Category III antiemetic active ingredients, i.e., bismuth subsalicylate, diphenhydramine hydrochloride, phosphorated carbohydrate, and scopolamine hydrobromide. The FDA concludes that the following data are required for the evaluation of the effectiveness or safety of these ingredients used as an OTC antiemetic:

a. *Bismuth subsalicylate.* The Panel noted that bismuth subsalicylate is not promoted as an antimotion sickness active ingredient and that motion sickness models would not be appropriate for testing this ingredient. Evaluation of the effectiveness of bismuth subsalicylate in reducing or controlling nausea and vomiting due to causes other than motion sickness requires well-controlled clinical trials in uniform groups of subjects with nausea and vomiting associated with specific conditions. Firms must indicate in their Category III Notification Statement which specific conditions are being tested, i.e., "for the prevention and/or treatment of nausea and vomiting associated with * * *." If it is desired to test bismuth subsalicylate as an agent to reduce or control nausea and vomiting due to motion sickness, the testing should be performed according to the effectiveness standards set forth above.

b. *Diphenhydramine hydrochloride.* The effectiveness of diphenhydramine hydrochloride as an antiemetic at its established dosage is not at issue, but clinical evidence is needed to establish that diphenhydramine hydrochloride is comparable in safety to dimenhydrinate for OTC antiemetic use. (See part I. paragraph B.10. above.)

c. *Phosphorated carbohydrate.* The Panel recommended, and the agency concurs, that phosphorated carbohydrate be tested according to the effectiveness standards set forth above. Firms must indicate in their Category III Notification Statement the indication or indications for which the drug is being tested. (See part II. paragraph B.3.c. above.)

d. *Scopolamine hydrobromide.* The agency concludes that scopolamine hydrobromide as used for motion sickness should be tested according to the effectiveness standards set forth above. (Also, see part I. paragraph B.9. above.)

Reference

(1) Brown, J. L., "Sensory Processess," *in* "The Pharmacological Basis of Medical Practice," 9th Ed., Edited by J. R. Brobeck, Williams & Wilkins, Baltimore, pp. 60–61, 1973.

The agency advises that the existing labeling requirements for OTC meclizine hydrochloride and cyclizine hydrochloride drug products contained

in § 201.37 and § 310.201(a)(6) which are superseded by the conditions established in this monograph will be withdrawn at the time that the monograph becomes effective.

The Food and Drug Administration has determined that this document does not contain an agency action covered by 21 CFR 25.1(b) and consideration by the agency of the need for preparing an environmental impact statement is not required.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C 553, 554, 702, 703, 704)), and under authority delegated to the Commissioner (21 CFR 5.1), the Commissioner is issuing as a tentative final order new Part 336 to read as follows:

PART 336—ANTIEMETIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Sec.

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

§ 336.1 Scope.

An over-the-counter antiemetic drug 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 336 in addition to each of the general conditions established in § 330.1 of this chapter.

§ 336.3 Definitions.

(a) *Age.* As used in this part, "infant" means a person under 2 years of age, "child" means a person 2 years to under 12 years of age, and "adult" means a person 12 years of age and older.

(b) *Antiemetic.* An agent that prevents or treats nausea and vomiting.

Subpart B—Active Ingredients

§ 336.10 Antiemetic active ingredients.

The active ingredients of the product consist of the following when used within the dosage limits established for each ingredient:

(a) Cyclizine hydrochloride.

(b) Dimenhydrinate.

(c) Meclizine hydrochloride.

Subpart C—[Reserved]

Subpart D—Labeling

§ 336.50 Labeling of antiemetic drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "antiemetic."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the phrase "for the prevention and treatment of nausea and vomiting associated with motion sickness."

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

(1) *For products containing any antihistamine ingredient identified in § 336.10.* (i) "Drowsiness sometimes results from taking this product. Do not operate motor vehicles or other machinery or equipment while taking this product."

(ii) "Avoid alcoholic beverages while taking this product."

(iii) "Do not take this product if you have asthma, glaucoma, or enlargement of the prostate gland except under the advice and supervision of a physician."

(2) *For products containing cyclizine hydrochloride identified in § 336.10(a).* "Do not give to children under 6 years of age except under the advice and supervision of a physician."

(3) *For products containing meclizine hydrochloride identified in § 336.10(c).* "Do not give to children under 12 years of age except under the advice and supervision of a physician."

(d) *Directions.* The labeling of the product contains the following statements under the heading "Directions," followed by "or as directed by a physician."

(1) *For products containing cyclizine hydrochloride identified in § 336.10(a).* Adult oral dosage is 50 milligrams every 4 to 6 hours, not to exceed 200 milligrams in 24 hours. For children 6 years of age and older, the oral dosage is 25 milligrams every 6 to 8 hours, not to exceed 75 milligrams in 24 hours.

(2) *For products containing dimenhydrinate identified in § 336.10(b).* Adult oral dosage is 50 to 100 milligrams every 4 to 6 hours, not to exceed 400 milligrams in 24 hours. For children 2 to under 6 years of age, the oral dosage is 12.5 to 25 milligrams every 6 to 8 years, not to exceed 75 milligrams in 24 hours. For children 6 to under 12 years of age, the oral dosage is 25 to 50 milligrams every 6 to 8 hours, not to exceed 150 milligramns in 24 hours.

(3) *For products containing meclizine hydrochloride identified in § 336.10(c).* Adult oral dosage is 25 to 50 milligrams once daily.

§ 336.80 Professional labeling.

(a) *For products containing dimenhydrinate identified in § 336.10(b).* The labeling of the product provided to health professionals (but not to the general public) may contain as an additional indication: "For the treatment of vertigo of motion sickness."

(b) *For products containing meclizine hydrochloride identified in § 336.10(c).* The labeling of the product provided to health professionals (but not to the general public) may contain as an additional indication: "For the treatment of vertigo."

Interested persons may file written objections and/or request an oral hearing before the Commissioner regarding this tentative final order on or before August 13, 1979. Request for an oral hearing must specify points to be covered and time requested. All objections and requests shall be submitted (preferably four copies and identified with the Hearing Clerk docket number found in brackets in the heading of this document) to the Hearing Clerk (HFA–305), Food and Drug Adminstration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857, and may be accompanied by a supporting memorandum or brief. Objections and request may be seen in the above office between the hours of 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register.**

In accordance with Executive Order 12044, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of the regulatory analysis assessment supporting this determination is on file with the Hearing Clerk, Food and Drug Administration.

Dated: July 6, 1979.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

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