DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310, 336, and 369

[Docket No. 78N-036A]

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

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing conditions under which over-the-counter (OTC) antiemetic drug products (products for the prevention and treatment of nausea and vomiting) are generally recognized as safe and effective and not misbranded. FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and all new data and information on antiemetic drug products that have come to the agency's attention. This final monograph is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: May 2, 1988.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drugs and Biologics (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of March 21, 1975 (40 FR 12902), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC antiemetic drug products, together with the recommendations of the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by June 19, 1975. Reply comments in response to comments filed in the initial comment period could be submitted by July 19, 1975.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration, Room 4-62, 5600 Fishers Lane, Rockville, MD 20857, after deletion of a small amount of trade secret information.

The agency's proposed regulation, in the form of a tentative final monograph, for OTC antiemetic drug products was published in the **Federal Register** of July 13, 1979 (44 FR 41064). Interested persons were invited to file by August 13, 1979, objections and/or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal. Final agency action occurs with the publication of this final monograph, which is a final rule establishing a monograph for OTC antiemetic drug products.

In the **Federal Register** of October 26, 1979 (44 FR 61610), the agency published a notice reopening the administrative record for OTC antiemetic drug products from October 26, 1979 to March 26, 1980 to permit manufacturers to submit, prior to the establishment of a final monograph, new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Interested persons were invited to submit comments on the new data on or before May 27, 1980. Data and information received after the administrative record was reopened are on display in the Dockets Management Branch.

In a notice published in the **Federal Register** of March 21, 1980 (45 FR 18398), the agency advised that it had also reopened the administrative record for OTC antiemetic drug products to allow for consideration of data and information that had been filed in the Dockets Management Branch after the date the administrative record had officially closed. The agency concluded that any new data and information filed prior to March 21, 1980 should be available to the agency in developing a final monograph.

The OTC procedural regulations (21 CFR 330.10) now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA is no longer using the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but is using instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III).

The agency advises that the conditions under which the drug products that are subject to this monograph will be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication in the **Federal Register.** Therefore, on or after May 2, 1988, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved new drug application (NDA). Further, any OTC drug products subject to this monograph that are repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In the tentative final monograph for OTC antiemetic drug products, the agency suggested that the conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the **Federal Register** and that the conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of whether further testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products may have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and further

reformulation is required, there could be a further delay in having a new product available for manufacture.

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is providing an effective date of 12 months after the date of publication of the final monograph in the **Federal Register**.

In response to the proposed rule on OTC antiemetic drug products, two consumer groups and three drug manufacturers submitted comments. Requests for oral hearing before the Commissioner were also received on three different issues. Copies of the comments and the hearing requests received are on public display in the Dockets Management Branch. Any additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notice published in the **Federal Register** of February 8, 1973 (38 FR 3614) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

I. The Agency's Conclusions on the Comments

A. General Comments on Antiemetic Drug Products.

1. One comment claimed that FDA has unreasonably narrowed the antiemetic monograph to focus only on products intended for prevention of motion sickness. The comment requested a hearing on this issue. The comment argued that FDA has improperly chosen to ignore the other causes of nausea on the theory that the term "nausea" is too vague to regulate. The comment further argued that FDA failed to review previously submitted data (Refs. 1 and 2) and to provide indications for products for the treatment of nausea and vomiting associated with conditions other than motion sickness.

FDA has not narrowed the scope of the antiemetic rulemaking to focus only on products intended for prevention of motion sickness. In the tentative final monograph, FDA specifically acknowledged that OTC antiemetics may also be used in the treatment of nausea and vomiting other than that associated with motion sickness. (See 44 FR 41068.) With the exception of the nausea claims associated with upset stomach or indigestion due to overindulgence in food and drink as discussed in comment 2 below, all other nausea and vomiting claims and the data to support them have been considered in this rulemaking. The two studies referred to by the comment were considered by the agency and are discussed in detail in comment 3 below. Because the record clearly demonstrates the agency's willingness to consider nausea and vomiting claims other than those associated with motion sickness, the agency concludes that a hearing on the issue of whether the agency has unreasonably narrowed the scope of the monograph is not warranted.

References

(1) Covarrubias, J., "Pepto-Bismol—Mexico Study," unpublished study no. 73069–195–76–02–339, Comment Nos. 0B0069 and C00081, Docket No. 78N–036A, Dockets Management Branch.

(2) DuPont, H. L., et al., "Symptomatic Treatment of Diarrhea with Bismuth Subsalicylate Among Students Attending a Mexican University," *Gastroenterology*, 73:715–718, 1977.

2. One comment claimed that FDA has unreasonably transferred nausea claims associated with "upset stomach" to the Advisory Review Panel on OTC Miscellaneous Internal Drug Products, arguing that the agency has intentionally been delaying consideration of the "upset stomach" issue. The comment added that this situation has resulted in confusion regarding where and how to submit documentation on the effectiveness of bismuth subsalicylate or any other ingredient in treating nausea associated with conditions other than motion sickness. The comment requested that data on the effectiveness of bismuth subsalicylate in treating nausea associated with "upset stomach and/or indigestion" be reviewed for inclusion in the OTC antiemetic final monograph. The comment also requested a hearing on this issue.

As the agency stated in the antiemetic tentative final monograph (44 FR 41067), "upset stomach" (which may include nausea, indigestion, pain, fullness, distention, or pressure) caused by overindulgence in food or drink was referred to the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (Miscellaneous Internal Panel). The agency does not believe it was unreasonable to refer these claims to the Miscellaneous Internal Panel because that Panel was charged with the responsibility of reviewing digestive aid and hangover remedy drug products. In its report on OTC Orally Administered Drug Products for Relief of Symptoms Associated With Overindulgence in Alcohol and Food, published in the **Federal Register** of October 1, 1982 (47 FR 43540), the Panel recommended Category I status for bismuth subsalicylate for the relief of upset stomach due to overindulgence in the combination of food and drink. The Panel also recommended that a claim for the relief of upset stomach "associated with nausea" due to such overindulgence be allowed for this ingredient. The agency's tentative conclusions on claims associated with overindulgence will be presented in a future **Federal Register** publication. If the agency concurs with the Panel findings, the antiemetic final monograph will be amended to include the nausea claim.

The agency has clarified on several occasions that the claims referred to by the comment, i.e., "upset stomach" or "indigestion," including the nausea symptom, are not being considered in the antiemetic rulemaking, but are being considered in the overindulgence rulemaking. The information in support of bismuth subsalicylate for these claims submitted by the comment to the antiemetic rulemaking has also been submitted to the appropriate docket. Agency review of that information is in progress. Because consideration of the "upset stomach" issue is pending completion of the rulemaking on OTC drug products for relief of symptoms of overindulgence in food and drink, the agency concludes that a hearing on this issue is not warranted at this time.

B. Comments on Antiemetic Active Ingredients

3. One comment cited five studies (Refs. 1 through 5) to support the effectiveness of bismuth subsalicylate in treating nausea of gastrointestinal origin and proposed the claims "nausea associated with diarrhea," "upset stomach associated with nausea," "nausea," and "queasiness" as Category I labeling for this condition. The comment also requested a hearing on the safety and effectiveness of bismuth subsalicylate for the prevention and treatment of nausea associated with diarrhea.

Three of the five studies (Refs. 1, 2, and 3) relate to the use of bismuth subsalicylate in treating symptoms associated with overindulgence in food and alcohol. (As discussed in comment 2 above, the agency's tentative conclusions on claims associated with

overindulgence will be presented in a future **Federal Register** publication.)

The remaining two studies (Refs. 4 and 5) provide data on the use of bismuth subsalicylate for treating nausea associated with diarrhea. However, these data are insufficient to establish the effectiveness of bismuth subsalicylate for such use. The agency's evaluation of these two studies follows.

Covarrubias Study (Ref. 4). This randomized parallel group study compared the effectiveness of a bismuth subsalicylate, salol, and zinc phenolsulfonate formulation, a bismuth subsalicylate formulation, and a kaolin-pectin formulation in relieving diarrhea. The subjects took two tablespoonsful of medication every ½ to 1 hour as needed until seven or eight doses were taken. Followup was at 6 hours after the initial dose and also at 12 hours, if no satisfactory relief was obtained at 6 hours. Of 144 patients studied, 111 had nausea associated with diarrhea (77 percent). The comment presented the results of a retrospective analysis of this study which specifically examined the three formulations' effectiveness in relieving nausea associated with diarrhea. Based on these results, the comment asserted that the bismuth subsalicylate formulation provides greater relief of nausea associated with diarrhea than the kaolin-pectin formulation, which was claimed to be not significantly better than a placebo.

The retrospective analysis presented the results for relief of nausea at 6 hours stratified by initial nausea severity and then statistically compared the results of bismuth subsalicylate and kaolin-pectin based on these stratifications. The sponsor's analyses considered only subjects for whom relief at 6 hours was reported. Sixteen subjects were listed as "not reported," and the results for these 16 subjects could change the results considerably. The p-value for the bismuth subsalicylate vs. kaolin-pectin comparison ranged from 0.06 to 0.29, depending on how the data were utilized, but even the best case does not show a statistically significant difference ($p<0.05$) between these two treatment groups. No information was provided concerning the results after an additional 6 hours for those subjects who did not obtain relief after the initial 6-hour period. Therefore, the study does not support the effectiveness of bismuth subsalicylate in relieving nausea associated with diarrhea.

DuPont Study. The comment submitted only the published version of the DuPont study (Ref. 5). However, the agency also evaluated detailed statistical analyses of this study, which were submitted to the rulemaking on OTC antidiarrheal drug products, because these analyses contained additional relevant data and information (Refs. 6 and 7).

This double-blind, placebo-controlled study compared the effectiveness of bismuth subsalicylate with placebo in the treatment of diarrhea among students attending a Mexican university. The study was conducted in two sequential phases. Students in Phase I were given a 30-milliliter (mL) dose of a bismuth subsalicylate preparation every ½ hour for eight doses for a total dose of 4.2 grams (g), and students in Phase II were given twice this dose. Objective parameters assessed were frequency, consistency, weight, and water content of the stools. Subjective relief of the symptoms of diarrhea, nausea, vomiting, and abdominal pain or cramps was also assessed.

Results presented in the statistical analyses indicate that the overall comparison of nausea relief for students in Phase I did not show a statistically significant difference between bismuth subsalicylate and placebo at the 5-percent confidence level. Additionally, a significant difference between bismuth subsalicylate and placebo is not reported in the statistical analyses when the results of Phase I are stratified by student status, by initial severity of diarrhea, and by prior duration of diarrhea. A significant difference between bismuth subsalicylate and placebo is reported when the results of Phase I are stratified by etiology, but this difference is questionable because patients not classified as to etiology (16 of 61 cases or 26 percent) were omitted from the analysis.

Phase II results are not discussed here because recent reports in the literature (Refs. 8 through 11) indicate that the salicylate moiety is readily absorbable from bismuth subsalicylate, and the agency believes that the higher dose in the Phase II study presents a potential for toxicity without a compensating therapeutic benefit. In addition, the manufacturer has indicated that it is not interested in promoting the higher dose of bismuth subsalicylate used in Phase II (Ref. 12).

Because the submitted data do not provide sufficient evidence to demonstrate effectiveness, bismuth subsalicylate has not been included in the final monograph for antiemetic drug products.

(Note: As discussed in comment 2 above, nausea claims associated with upset stomach, indigestion, or overindulgence in food and alcohol are pending completion of other OTC drug rulemakings.)

After considering all available material relevant to the safety and effectiveness of bismuth subsalicylate for use in the prevention and treatment of nausea associated with diarrhea, the agency concludes that there are insufficient grounds to support a hearing on this matter. The evaluations of the Covarrubias and DuPont studies presented above point out significant deficiencies in these studies, so that these studies do not demonstrate the effectiveness of bismuth subsalicylate for this indication. There is a lack of substantial evidence to show that bismuth subsalicylate is effective in preventing or treating nausea associated with diarrhea. Accordingly, a hearing to discuss this issue would not be useful and is not warranted.

References

(1) Berkowitz, J.M., "Bismuth Subsalicylate in Excessive Alcohol/Food Intake," unpublished study No. 79023–195.73.438, in Comment No. C00081, Docket No. 78N–036A, Dockets Management Branch.

(2) Newsom, J.H., "Evaluation of Bismuth Subsalicylate in Relieving Symptoms of Indigestion," unpublished study No. 76031–195–76–11–497, in Comment No. C00081, Docket No. 78N–036A, Dockets Mangement Branch.

(3) Davis, S.S., "The Effectiveness of Pepto-Bismol in Gastrointestinal Upsets," unpublished study No. 73075–195.7602–347, in Comment No. C00081, Docket No. 78N–036A, Dockets Management Branch.

(4) Covarrubias, J., "Pepto-Bismol-Mexico Study," unpublished study No. 73069–195–76–02–339, in Comment Nos. 0B0069 and C00081, Docket No. 78N–036A, Dockets Management Branch.

(5) DuPont, H.L., et al., "Symptomatic Treatment of Diarrhea with Bismuth Subsalicylate Among Students Attending a Mexican University," *Gastroenterology*, 73:715–718, 1977.

(6) Comment No. C00074, Docket No. 78N–036D, Dockets Management Branch.

(7) Comment No. 0B052A, Docket No. 78N–036D, Dockets Management Branch.

(8) Feldman, S., et al., "Absorption of Salicylate from a Bismuth Subsalicylate Antidiarrheal Preparation (Pepto-Bismol)," *Clinical Pharmacology and Therapeutics*, 27:252, 1980.

(9) Feldman, et al., "Salicylate Absorption from a Bismuth Subsalicylate Preparation," *Clinical Pharmacology and Therapeutics*, 29:788–792, 1981.

(10) Unsigned Article, "Salicylate in Pepto-Bismol," *The Medical Letter on Drugs and Therapeutics*, 22:63, 1980.

(11) Pickering, L.K., et al., "Absorption of Salicylate and Bismuth from a Bismuth Salicylate-Containing Compound (Pepto-Bismol)," *The Journal of Pediatrics*, 99:654–656, 1981.

(12) Memorandum of meeting between Norwich-Eaton Pharmaceuticals and Division of OTC Drug Evaluation Staff, February 25, 1982, copy included in OTC Volume 690AFM.

4. One comment objected to the agency's conclusions that cyclizine hydrochloride, meclizine hydrochloride, and dimenhydrinate are safe for use in OTC antiemetic drug products for the prevention and treatment of nausea and vomiting associated with motion sickness and requested that these ingredients be reclassified to Category II. The comment claimed that mutagenicity and carcinogenicity data on these ingredients are insufficient to meet the agency's NDA safety requirements and, therefore, do not meet the statutory or scientific criteria for general recognition of safety.

Cyclizine hydrochloride, meclizine hydrochloride, and dimenhydrinate are currently the subjects of approved NDA's and the agency is unaware of any data demonstrating that any of these ingredients is a potential carcinogen or mutagen. Further, none of these drugs has been selected for bioassay testing as part of the National Toxicology Program's Carcinogenicity Testing Program (Ref. 1). Because the comment has not provided a sufficient basis for reclassifying cyclizine hydrochloride, meclizine hydrochloride, and dimenhydrinate to Category II, these ingredients are being included in the final monograph, based on the evidence available at the present time. If future evidence, e.g., results of bioassay testing, demonstrates an ingredient to be unsafe for OTC use, the agency will act to remove products containing that ingredient from the marketplace.

Reference

(1) Copy of a computer printout from the National Toxicology Program—Carcinogenicity Testing Program, OTC Volume 090AFM, Docket No. 78N–036A, Dockets Management Branch.

5. One comment requested reclassification of phosphorated carbohydrate from Category III to Category I and stated that data submitted to the Panel (Ref. 1) demonstrate the effectiveness of this ingredient. In addition, the comment submitted a published study claimed to show phosphorated carbohydrate's "mode of action" (Ref. 2) and two new clinical studies (420–3A and 420–4B) claimed to establish phosphorated carbohydrate's effectiveness in relieving nausea and vomiting (Ref. 3).

After reviewing and evaluating all of the available data, the agency concludes that they are insufficient to reclassify phosphorated carbohydrate in Category I. In the tentative final monograph (44 FR 41071), the agency concurred with the Panel that the material submitted on phosphorated carbohydrate was insufficient to demonstrate its effectiveness in the management of nausea and vomiting. The agency reaffirms that decision.

The submitted study on phosphorated carbohydrate's mechanism of action does not provide adequate evidence of effectiveness (Ref. 2). The study merely suggests that phosphorated carbohydrate may act as an antiemetic by inhibiting gastric emptying, but does not specifically discuss its effectiveness for this use. Also, the study included only five patients and was not a well-controlled clinical study in an appropriate target population.

Study 420–3A was a randomized, double-blind, parallel, placebo-controlled study designed to show the effectiveness of phosphorated carbohydrate for the control of vomiting due to nonspecific gastroenteritis in children aged 2 to 12 years (Ref. 3). Study 420–4B was similarly designed to show the effectiveness of phosphorated carbohydrate for the relief of nausea and vomiting in early pregnancy (Ref. 3). Both studies are inadequate because of unequal distribution of patients among investigators, which subsequently biased the results of the studies. The agency's detailed comments and evaluation of the data are on file with the Dockets Management Branch (Ref. 4).

Because the submitted data do not provide sufficient evidence to demonstrate effectiveness, phosphorated carbohydrate has not been included in the final monograph for OTC antiemetic drug products. However, the agency is aware that a manufacturer of this product is conducting additional studies to prove the effectiveness of phosphorated carbohydrate, and the results will be submitted to the agency in the near future (Refs. 5 and 6). If data establishing effectiveness of phosphorated carbohydrate as an OTC antiemetic are subsequently submitted to the agency, procedures to amend the monograph may be initiated under § 330.10(a)(12) of the regulations (21 CFR 330.10(a)(12)). Regulatory policy for nonmonograph products is set forth in the **Federal Register** of May 13, 1980 (see 45 FR 31424 to 31425).

References

(1) OTC Volume 090051.

(2) Houston, J.B. and G. Levy, "Effect of Carbonated Beverages and of an Antiemetic Containing Carbohydrate and Phosphoric Acid on Riboflavin Bioavailability and Salicylamide Biotransformation in Humans," *Journal of Pharmaceutical Sciences*, 64:1504–1507, 1975.

(3) Studies 420–3A and 420–4B, in Comment No. CP, Docket No. 78N–036A, Dockets Management Branch.

(4) Letter from W.E. Gilbertson, FDA, to R.F. Panner, William H. Rorer, Inc., coded LET002, Docket No. 78N–036A, Dockets Management Branch.

(5) Memorandum of telephone conversation between R. F. Panner, William H. Rorer, Inc., and D. L. Myers, FDA, September 10, 1982, coded MT0004, Docket No. 78N–036A, Dockets Management Branch.

(6) Memorandum of telephone conversation between R. F. Panner, William H. Rorer, Inc., and E. McGoodwin, FDA, August 26, 1986, copy included in OTC Volume 090AFM.

C. Comments on Labeling of Antiemetic Drug Products

6. One comment pointed out that the dimenhydrinate dose for children 2 to under 6 years of age was incorrectly stated in the tentative final monograph as every 6 to 8 years, instead of every 6 to 8 hours.

This error has been corrected in the final monograph.

7. One comment suggested that the warning in proposed § 336.50(c)(1)(i), which reads, "Drowsiness sometimes results from taking this product. Do not operate motor vehicles or other machinery or equipment while taking this product," be modified to include the word "dangerous" before the word machinery. The comment contended that this would exclude machinery such as small appliances from the warning.

The agency is not including the comment's suggested change in this final monograph because warning consumers to use care only when operating "dangerous" machinery may not be adequate. Consumers may not consider some machinery dangerous if operated by an alert individual, but any machinery is potentially dangerous if operated by a person who is drowsy.

In the tentative final monograph for OTC antihistamine drug products, published in the **Federal Register** of January 15, 1985 (50 FR 2200), the warning required for antihistamine-containing drug products regarding operating motor vehicles or machinery was combined with the warnings regarding drowsiness and alcoholic beverages. The agency concluded that combining these related warnings would be beneficial to consumers. In addition, the agency recognizes that sedative drugs and tranquilizers are known to have additive effects to the drowsiness effect of antihistamine drug products (Refs. 1 and 2). The agency concludes that the drowsiness warning should include sedatives and tranquilizers as other drugs that may intensify the drowsiness effect of antihistamines. Further, in the tentative final monograph for OTC antihistamine drug products, the agency recognized that there are

differences with respect to the degree of drowsiness depending on the ingredient and that a stronger warning regarding drowsiness may be necessary for certain ingredients (see 50 FR 2210). The agency recognizes that Roth and Tabachnick (Ref. 3) have classified the sedative effect for diphenhydramine and dimenhydrinate as "marked" whereas the sedative effect for meclizine and cyclizine is classified as "slight." Therefore, the word "marked" is being included in the drowsiness warning for the ingredients diphenhydramine hydrochloride and dimenhydrinate. The agency does not find it necessary to add the term "slight" to the existing warning for the other ingredients. Based on the above discussion the warnings have been revised in this final monograph to read as appropriate: "May cause drowsiness;" or "May cause marked drowsiness;" "alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery." Although the warning in proposed § 336.50(c)(1)(i) included the words "machinery or equipment," the revised warning does not include the word "equipment" because the use of the word "machinery" sufficiently conveys the meaning intended by the warning.

References

(1) Douglas, W.W., "Histamine and 5-Hydroxytryptamine (Serotonin) and Their Agonists," *In* "The Pharmacological Basis of Therapeutics," 7th Ed., edited by A.G. Gilman et al., MacMillan Publishing Co., New York, p. 621, 1985.

(2) "Histamine and Antihistamines," in "Remington's Pharmaceutical Sciences," 17th Ed., edited by A.R. Gennero, Mack Publishing Co., Easton, PA, pp. 1125–1126, 1985.

(3) Roth, F.E., and I.I.A. Tabachnick, "Histamine and Antihistamine," *In* "Drill's Pharmacology in Medicine," 4th Ed., edited by J.R. DiPalma, McGraw-Hill Book Co., NY, p. 1009, 1971.

8. One comment noted that the warnings in proposed § 336.50(c) (2) and (3) for cyclizine hydrochloride and meclizine hydrochloride provide for the administration of these drugs to children of any age "under the advice and supervision of a physician," but a similar provision was not made for dimenhydrinate. The comment requested that a statement be added to the monograph to provide for the administration of dimenhydrinate to children under 2 years of age under the advice and supervision of a physician.

In the tentative final monograph, the agency proposed a warning for cyclizine hydrochloride not to give to children under 6 years of age and for meclizine hydrochloride not to give to children under 12 years of age, except under the advice and supervision of a physician (§ 336.50(c) (2) and (3)). The agency also proposed directions for use for dimenhydrinate for children 2 to under 6 years of age (§ 336.50(d)(2)), but inadvertently did not include a warning against giving dimenhydrinate to children under 2 years of age except under the advice and supervision of a physician. The agency agrees with the comment that a warning of this type should be required for products containing dimenhydrinate. Accordingly, the statement "Do not give to children under 2 years of age unless directed by a doctor" has been added to the warnings for dimenhydrinate.

9. One comment requested that the claim "dizziness of motion sickness" be included in the OTC labeling indications for dimenhydrinate, stating that dizziness is a self-diagnosable symptom of motion sickness and that the consumer should have the option to self-medicate for this symptom.

While dizziness or vertigo could be a symptom of conditions other than motion sickness, e.g., Meniere's syndrome, the agency agrees with the comment that dizziness specifically associated with motion sickness is a self-diagnosable symptom that is amenable to treatment with OTC drugs. Sources in the scientific literature confirm that dizziness or vertigo is a symptom of motion sickness (Refs. 1 and 2) and the effectiveness of dimenhydrinate in preventing or treating the symptom of dizziness associated with motion sickness has been adequately demonstrated in clinical trials (Refs. 3 and 4). Furthermore, in the Federal Register of July 29, 1977 (42 FR 38645), FDA published a Drug Efficacy Study Implementation (DESI) notice stating that prescription dimenhydrinate drug products in suppository or sterile solution form suitable for rectal or parenteral administration, respectively, are effective "for the prevention and treatment of the nausea, vomiting, or vertigo of motion sickness."

The literature sources cited above (Refs. 3 and 4) also demonstrate that cyclizine hydrochloride, diphenhydramine hydrochloride, and meclizine hydrochloride are effective in preventing or treating dizziness associated with motion sickness. Other supporting evidence for the effectiveness of these drugs in preventing or treating dizziness associated with motion sickness was contained in submissions to the Panel (Refs. 5, 6, and 7).

Accordingly, the indications in this final monograph for cyclizine hydrochloride, dimenhydrinate, diphenhydramine hydrochloride, and meclizine hydrochloride include the symptom of dizziness associated with motion sickness. The professional labeling also includes the indication "For the treatment of vertigo of motion sickness" for cyclizine hydrochloride and diphenhydramine hydrochloride.

References

(1) Reason, J.T., and J.J. Brand, "Motion Sickness," Academic Press, London, pp. 38–82, 1975.

(2) Money, K.E., "Motion Sickness," Physiological Reviews, 50:1–39, 1970.

(3) Arner, O., et al., "Antihistamines in Sea Sickness," *Archieves Internationales de Pharmacodynamie*, 117:404–418, 1958.

(4) 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.

(5) OTC Volume 090040.

(6) OTC Volume 090041.

(7) OTC Volume 090066.

II. Summary of Significant Changes

1. Bismuth subsalicylate is not being included in the monograph at this time pending review of data submitted to the rulemaking on OTC drug products for relief of symptoms associated with overindulgence in alcohol and food. (See comment 3 above.)

2. In the tentative final monograph for OTC antiemetic drug products (44 FR 41066), FDA tentatively concluded that diphenhydramine hydrochloride should be Category III based on its apparent chemical and pharmacological similarity to dimenhydrinate. Although the effectiveness of diphenhydramine hydrochloride for use as an antiemetic in motion sickness was not in question, the agency concluded that additional evidence was needed to establish that the sedative effects of diphenhydramine hydrochloride are not significantly different from those of dimenhydrinate. The agency proposed that clinical studies be conducted to compare diphenhydramine hydrochloride with dimenhydrinate and to a placebo for the depth and length of drowsiness. No new data on diphenhydramine hydrochloride were submitted in response to the antiemetic tentative final order. However, subsequent to that publication, FDA made a final decision concerning the OTC marketing of diphenhydramine hydrochloride as an antitussive drug product (44 FR 51512), indicating that the risk of drowsiness alone as a side effect does not seem to

provide sufficient reason to restrict a drug to prescription use. The agency explained that drowsiness itself does not cause harm, and that it is only when the individual tries to undertake a task requiring alertness, such as driving a car, that risk is posed. In addition, FDA has approved a supplemental NDA for diphenhydramine hydrochloride to be marketed as an OTC antitussive and has proposed diphenhydramine hydrochloride as Category I in the tentative final monograph for OTC antihistamine drug products (50 FR 2206). Accordingly, FDA concludes that the risks presented by diphenhydramine hydrochloride for use as an antiemetic are not sufficient to warrant continued restriction to prescription status, provided that adequate warnings concerning the side effect of drowsiness are included in the labeling. FDA believes that the drowsiness and alcohol warning included in this final monograph is sufficient to warn consumers of the drowsiness side effect of diphenhydramine hydrochloride. (See comment 7 above.)

The agency, therefore, is including diphenhydramine hydrochloride in this final monograph for use as an OTC antiemetic at an adult dosage of 25 to 50 milligrams (mg) every 4 to 6 hours not to exceed 300 mg in 24 hours, and for children 6 to under 12 years of age at a dosage of 12.5 to 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. In addition, the statement "Do not give to children under 6 years of age unless directed by a doctor" is included in the warnings for diphenhydramine hydrochloride.

3. Phosphorated carbohydrate is not being included in the monograph at this time as an ingredient for use as an OTC antiemetic. (See comment 5 above.)

4. Scopolamine hydrobromide was listed in the tentative final monograph as a Category III ingredient (44 FR 41070). Because no additional data were submitted to support the general recognition of safety and effectiveness of this ingredient as an OTC antiemetic, it is not included in the final monograph and is considered a nonmonograph ingredient.

5. The drowsiness and alcohol warnings for antiemetics containing antihistamines have been revised and combined to read, "May cause drowsiness;" or "May cause marked drowsiness;" "alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery." The agency intends to include this revised warning in an amendment to the tentative final monograph for OTC antihistamine drug products, to be published in a future issue of the Federal Register. (See comment 7 above.)

6. The warning "Do not give to children under 2 years of age unless directed by a doctor" has been added for products containing dimenhydrinate. (See comment 8 above.)

7. The indication "For the prevention and treatment of nausea and vomiting associated with motion sickness" has been revised to read, "For the prevention and treatment of the nausea, vomiting, or dizziness associated with motion sickness." (See comment 9 above.)

8. The warning regarding the use of antihistamine drugs in persons with an enlarged prostate gland has been amended for clarity to include the presenting symptom "difficulty in urination." In addition, the warning has been expanded to be consistent with the warning proposed in the tentative final monograph for OTC antihistamine drug products to read "Do not take this product if you have asthma, glaucoma, emphysema, chronic pulmonary disease, shortness of breath, difficulty in breathing, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor." (For discussion of the need to expand the warning, see the Federal Register of January 15, 1985; 50 FR 2215.)

9. In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs to substitute the word "doctor" for "physician" in OTC drug monographs on the basis that the word "doctor" is more commonly used and better understood by consumers. Based on comments received to these proposals, the agency has determined that final monographs and any applicable OTC drug regulation will give manufacturers the option of using either the word "physician" or the word "doctor." This final monograph includes that option. In addition, the phrase "except under the advice and supervision of a physician" has been changed to read, "unless directed by a doctor."

10. The agency has redesignated proposed Subpart D as Subpart C and has placed the labeling sections of the monograph in Subpart C.

III. The Agency's Final Conclusions on OTC Antiemetic Drug Products

Based on the available evidence, the agency is issuing a final monograph establishing conditions under which OTC antiemetic drug products are generally recognized as safe and effective and not misbranded. FDA has determined that cyclizine hydrochloride, dimenhydrinate, diphenhydramine hydrochloride, and meclizine hydrochloride are generally recognized as safe and effective for OTC use as antiemetic drugs. Any drug product marketed for use as an OTC antiemetic that is not in conformance with the monograph (21 CFR Part 336) will be considered a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)) and misbranded under section 502(a) of the act (21 U.S.C. 352(a)) and may not be marketed for this use unless it is the subject of an approved NDA.

In the Federal Register of May 1, 1986 (51 FR 16258), the agency published a final rule changing its labeling policy for stating the indications for use of OTC drug products. Under the final rule, the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either (1) the specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "APPROVED USES"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "APPROVED USES"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "APPROVED USES," plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All required OTC drug labeling other than indications for use (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under an OTC drug monograph. The final rule in this document is subject to the final rule revising the labeling policy.

The agency has examined the economic consequences of this final rule in conjunction with other rules resulting from the OTC drug review. In a notice published in the Federal Register of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this final rule for OTC

antiemetic drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act, Pub. L. 96–354. That assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, the requirement for a Regulatory Flexibility Analysis under the Regulatory Flexibility Act does not apply to this final rule for OTC antiemetic drug products because the proposed rule was issued prior to January 1, 1981, and is therefore exempt. However, this particular rulemaking for OTC antiemetic drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

In the antiemetic tentative final monograph (44 FR 41068), the agency proposed that the existing regulations in 21 CFR 201.307 and 21 CFR 310.201(a)(6), which are superseded by the conditions established in this monograph, would be withdrawn at the time the final monograph became effective. The existing regulations in § 201.307 are based on available animal data that demonstrated that benzhydryl piperazine antihistamines (meclizine and cyclizine) exerted a teratogenic response in animals. However, FDA concluded in the tentative final monograph that, in light of more recent epidemiological data, a pregnancy warning would not be needed.

Subsequent to the publication of the antiemetic tentative final monograph, a general pregnancy-nursing warning for all OTC drug products intended for systemic absorption (21 CFR 201.63) became effective on December 5, 1983. Most manufacturers of OTC drug products containing cyclizine or meclizine have chosen to include the general pregnancy-nursing warning required by § 201.63 in the labeling of these drug products rather than the warning required by § 201.307. Also subsequent to publication of the antiemetic tentative final monograph, the agency has evaluated additional human epidemiological data (Ref. 1) and has determined that there is sufficient human experience to conclude that cyclizine and meclizine have not been established to be human teratogens. Therefore, based on these human data, the agency has concluded that the general pregnancy warning required by § 201.63 is sufficient for antiemetic drug products containing cyclizine or meclizine and a more specific warning for these drugs is not necessary. The requirements of § 201.307 with respect to cyclizine hydrochloride and meclizine hydrochloride are superseded by this document. The agency will address removal of § 201.307 in a future **Federal Register** publication.

The agency is removing § 310.201(a)(6) because the provisions of that regulation are superseded by the requirements of the antiemetic final monograph (Part 336). For this same reason, those portions of § 369.20 and § 369.21 applicable to meclizine and cyclizine and their salts are also being removed.

Reference

(1) Rosa, F., "Benzhydrylpiperazine (Cyclizines) Terato-Epidemiology," unpublished draft, June 25, 1985, in OTC Volume 090AFM, Docket No. 78N–036A, Dockets Management Branch.

List of Subjects

21 CFR Part 310

New drugs; Prescription exemption.

21 CFR Part 336

Labeling, Over-the-counter drugs, Antiemetic drug products.

21 CFR Part 369

OTC drugs; Warning and caution statements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations is amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR Part 310 continues to read as follows:

Authority: Secs. 502, 503, 505, 701, 52 Stat. 1051, 1052, 1053, 1055 as amended (21 U.S.C. 352, 353, 355, 371); 5 U.S.C. 553; 21 CFR 5.10 and. 5.11.

§ 310.201 [Amended]

2. In Subpart C, § 310.201 *Exemption for certain drugs limited by new-drug applications to prescription sale* is amended by removing paragraph (a)(6), "Meclizine hydrochloride," and reserving it for future use.

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

3. By adding new Part 336, to read as follows:

Subpart A—General Provisions

Sec.
336.1 Scope.
336.3 Definition.

Subpart B—Active Ingredients

336.10 Antiemetic active ingredients.

Subpart C—Labeling

336.50 Labeling of antiemetic drug products.
336.80 Professional labeling.

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

Subpart A—General Provisions

§ 336.1 Scope.

(a) 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 and each of the general conditions established in § 330.1.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 336.3 Definition.

As used in this part:

Antiemetic. An agent that prevents or treats nausea and vomiting.

Subpart B—Active Ingredients

§ 336.10 Antiemetic active ingredients.

The active ingredient of the product consists of any of the following when used within the dosage limits established for each ingredient in § 336.50(d):

(a) Cyclizine hydrochloride.

(b) Dimenhydrinate.

(c) Diphenhydramine hydrochloride.

(d) Meclizine hydrochloride.

Subpart C—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 states the following under the heading "Indications," "For the prevention and treatment of the nausea, vomiting, or dizziness associated with motion sickness." Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph (b), may also be used, as provided in § 330.1(c)(2), subject to the

provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

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

(1) *For products containing any ingredient identified in § 336.10.* "Do not take this product if you have asthma, glaucoma, emphysema, chronic pulmonary disease, shortness of breath, difficulty in breathing, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

(2) *For products containing cyclizine hydrochloride identified in § 336.10(a).* "Do not give to children under 6 years of age unless directed by a doctor."

(3) *For products containing dimenhydrinate identified in § 336.10(b).* "Do not give to children under 2 years of age unless directed by a doctor."

(4) *For products containing diphenhydramine hydrochloride identified in § 336.10(c).* "Do not give to children under 6 years of age unless directed by a doctor."

(5) *For products containing meclizine hydrochloride identified in § 336.10(d).* "Do not give to children under 12 years of age unless directed by a doctor."

(6) *For products containing cyclizine hydrochloride identified in § 336.10(a) or meclizine hydrochloride identified in § 330.10(d).* "May cause drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery."

(7) *For products containing dimenhydrinate identified in § 336.10(b) or diphenhydramine hydrochloride identified in § 336.10(c).* "May cause marked drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions":

(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 or as directed by a doctor. 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 or as directed by a doctor.

(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 or as directed by a doctor. 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 milligrams in 24 hours or as directed by a doctor. For children 2 to under 6 years of age, the oral dosage is 12.5 to 25 milligrams every 6 to 8 hours, not to exceed 75 milligrams in 24 hours or as directed by a doctor.

(3) *For products containing diphenhydramine hydrochloride identified in § 336.10(c).* Adult oral dosage is 25 to 50 milligrams every 4 to 6 hours, not to exceed 300 milligrams in 24 hours or as directed by a doctor. For children 6 to under 12 years of age, the oral dosage is 12.5 to 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours or as directed by a doctor.

(4) *For products containing meclizine hydrochloride identified in § 336.10(d).* Adult oral dosage is 25 to 50 milligrams once daily or as directed by a doctor.

(e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this section.

§ 336.80 Professional labeling.

The labeling provided to health professionals (but not to the general public) may contain the following additional indications.

(a) *For products containing cyclizine hydrochloride, dimenhydrinate, and diphenhydramine hydrochloride identified in § 336.10 (a), (b), and (c).* "For the treatment of vertigo of motion sickness."

(b) *For products containing meclizine hydrochloride identified in § 336.10(d).* "For the treatment of vertigo."

PART 369—INTERPRETATIVE STATEMENTS RE WARNINGS ON DRUGS AND DEVICES FOR OVER-THE-COUNTER SALE

4. The authority citation for 21 CFR Part 369 continues to read as follows:

Authority: Secs. 502, 503, 506, 507, 701, 52 Stat. 1050–1052 as amended, 55 Stat. 851, 59 Stat. 463 as amended, 52 Stat. 1055–1056 as amended (21 U.S.C. 352, 353, 356, 357, 371); 21 CFR 5.10 and 5.11.

§ 369.20 [Amended]

5. In Subpart B, § 369.20 *Drugs; recommended warning and caution statements* is amended by removing that portion of the entry for "ANTIHISTAMINICS, ORAL" pertaining specifically to cyclizine.

§ 369.21 [Amended]

6. In Subpart B, § 369.21 *Drugs; warning and caution statements required by regulations* is amended by removing that portion of the entry for "ANTIHISTAMINICS, ORAL (PHENYLTOLOXAMINE DIHYDROGEN CITRATE, MECLIZINE HYDROCHLORIDE, DOXYLAMINE SUCCINATE, CHLOROTHEN CITRATE, CYCLIZINE HYDROCHLORIDE, AND CHLORCYCLIZINE HYDROCHLORIDE PREPARATIONS)" Pertaining specifically to cyclizine, cyclizine hydrochloride, meclizine, and meclizine hydrochloride.

Dated: March 1, 1987.

Frank E. Young,

Commissioner of Food and Drugs.

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