DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 338

[Docket No. 75N-0244]

Nighttime Sleep-Aid 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) nighttime sleep-aid drug products 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 nighttime sleep-aid drug products that have come to the agency's attention. This final monograph deals only with single ingredient nighttime sleep-aid drug products and is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: February 14, 1990.

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

SUPPLEMENTARY INFORMATION: In the **Federal Register** of December 8, 1975 (40 FR 57292), 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 nighttime sleep-aid drug products, together with the recommendations of the Advisory Review panel on OTC Sedative, Tranquilizer, and Sleep-aid Drug Products (Sleep-aid Panel), 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 March 8, 1976. Reply comments in response to comments filed in the initial comment period could be submitted by April 8, 1976.

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, Rm. 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 nighttime sleep-aid drug products was published in the **Federal Register** of June 13, 1978 (43 FR 25544). Interested persons were invited to file by August 14, 1978 written objections and requests for an 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 nighttime sleep-aid drug products.

In the **Federal Register** of October 26, 1979 (44 FR 61610), the agency published a notice reopening the administrative record for OTC nighttime sleep-aid 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 18399), the agency advised that it had also reopened the administrative record for OTC nighttime sleep-aid drug products to allow for consideration of data and information that had been filed in the Dockets Management Branch during the period from August 14, 1978, to October 26, 1979. 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.

In the **Federal Register** of April 23, 1982 (47 FR 17740), the agency published a notice announcing an enforcement policy to permit the OTC marketing of diphenhydramine as an ingredient in OTC nighttime sleep-aid drug products pending the establishment of a final monograph on OTC nighttime sleep-aid drug products. In that notice, the Commissioner concluded that there were no unresolved safety or effectiveness issues relating to the use of diphenhydramine as an OTC nighttime sleep-aid and that it would be inappropriate, and not in the public interest, to continue to bar the interim marketing of such products.

The OTC drug 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 February 14, 1990, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. Further, any OTC drug product subject to this monograph that is repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In the tentative final monograph for OTC nighttime sleep-aid 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 nighttime sleep-aid drug products, four consumers, two consumer groups, six drug manufacturers, one drug manufacturer association, and one consultant representing four different drug manufacturers submitted comments. Requests for oral hearing before the Commissioner were also received on 12 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.

In proceeding with this final monograph, the agency has considered all objections, requests for oral hearings, and the changes in the procedural regulations. In light of the changes in the OTC drug review procedural regulations and the withdrawal of methapyrilene from the marketplace (see below), many of the objections filed in response to the agency's proposed regulation on OTC nighttime sleep-aid drug products are no longer applicable, e.g., comments on testing guidelines and on methapyrilene. In those cases where the agency has agreed with submitted objections and has revised the final monograph accordingly, the Commissioner concludes that any requests for hearing are moot. Therefore, such hearing requests are not discussed in the following responses to comments.

One comment requested hearings on several aspects of the rule if the Commissioner, in making his decisions, relied upon evidence that was not in the public domain. The Commissioner advises that the agency's decisions in this rulemaking have been based entirely on the administrative record, which is publicly available in the Dockets Management Branch. Therefore, the Commissioner concludes that the comment is no longer requesting hearings on those issues. All other requests for hearing are discussed below.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notice published in the **Federal Register** of August 9, 1972 (37 FR 16029), or to additional information that has come to the agency's attention since publication of the notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

I. The Agency's Conclusions on the Comments

A. General Comments on OTC Nighttime Sleep-Aid Drug Products

1. One comment requested that the agency not remove nighttime sleep-aid drug products from the OTC market.

The tentative final monograph on nighttime sleep-aid drug products (43 FR 25544) did not propose to remove this entire class of drug products from the OTC market. The agency recognized the usefulness of this class of drugs, but concluded that the data available at that time were not sufficient for FDA to determine that any specific ingredients in this class of drugs were generally recognized as safe and effective. Since that time, additional data have been submitted to the OTC drug review to support the safety and effectiveness of diphenhydramine hydrochloride and diphenhydramine monocitrate (now named diphenhydramine citrate), and these ingredients are included in the final monograph for OTC nighttime sleep-aid drug products. In addition, products containing doxylamine succinate are marketed OTC as a nighttime sleep-aid under approved new drug applications (NDA's).

2. One comment argued that the Commissioner had failed to follow the prescribed procedures in issuing the tentative final monograph on OTC nighttime sleep-aids and that it is without legal authority. The comment also contended that the tentative final monograph is arbitrary, capricious, and not supported by substantial evidence and requested a hearing on this issue.

At the time of publication of the panel's report and recommended monograph in the **Federal Register** of December 8, 1975 (40 FR 57292), § 330.10(a)(6) provided for a comment period of 60 days after publication of a panel's report and recommended monograph, and a period of 30 days from the last day of the comment period for reply comments to be filed. In the report, the agency allowed for a comment period of 90 days, which conforms with current 330.10(a)(6). Section 330.10(a)(7) provided that after reviewing all comments and reply comments, a tentative final monograph would be published in the **Federal Register**. The agency received comments and reviewed them. In the **Federal Register** of June 13, 1978 (40 FR 57292), the agency responded to the comments in the tentative final monograph. Section 330.10(a)(7) has been subsequently expanded to require review of new data prior to publication of a tentative final monograph.

The comment does not specify what procedures it alleges that the Commissioner failed to follow and the agency is not aware of any. Therefore, the agency concludes that it followed the prescribed procedures set forth in 21 CFR 330.10(a)(6) and (7) for publishing a tentative final monograph on OTC nighttime sleep-aid drug products. The agency rejects the comment's contention that the tentative final monograph is without legal authority. The legal authority for this rulemaking process is provided by the Federal Food, Drug, and Cosmetic Act (the act), as cited in the "Authority" paragraph which immediately precedes the monograph. The agency's conclusions reached in the tentative final monograph are supported and well documented with references publicly available in the administrative record for this rulemaking. Therefore, the agency concludes the comment's contention is not valid. The Commissioner also concludes that a hearing on this issue is not warranted.

3. One comment objected to the statement in the tentative final monograph "that OTC drugs should contain only such inactive ingredients as are known to be safe and are necessary for pharmaceutical formulation" (43 FR 25544 at 25590). The comment contended that this statement is without sanction of law and is inconsistent with other FDA regulations. The comment requested revocation of the statement.

The statement in question was part of the preamble and not part of the tentative final monograph; thus, it need

not be "revoked" as the comment requested. The act and the regulations implementing the OTC drug review provide clear authority for requiring that inactive ingredients be safe. The act requires all drugs to be both safe and effective for their intended use. Thus, inactive ingredients that are included in drug products also need to be safe in order for the product to conform to the requirements of the act. The OTC drug review regulations in § 330.1(e) further state that OTC drug products should contain "only suitable inactive ingredients which are safe in the amounts administered and do not interfere with the effectiveness of the preparation * * *." The food ingredient GRAS (generally recognized as safe) list in 21 CFR Part 182 includes most of the common inactive ingredients, including flavors. Color additives are already regulated under section 706 of the act (21 U.S.C. 376) and the implementing regulations in 21 CFR Parts 70 through 82. An ingredient, whether active or inactive, should be included in a drug product only if it provides a benefit and is therefore "necessary." Typically, inactive ingredients are necessary for a drug product's pharmaceutical formulation during the manufacturing process and for making the product acceptable to the user in terms of taste, appearance, and aroma. Such ingredients may be used provided they do not interfere with the product's effectiveness.

4. One comment urged the agency to require long-term carcinogenicity studies on all the ingredients placed in Category III as nighttime sleep-aids before they are given general recognition of safety.

FDA is aware that all of the antihistamine ingredients placed in Category III in the tentative final monograph on OTC nighttime sleep-aid drug products (43 FR 25544 at 25579), except for phenyltoloxamine dihydrogen citrate, have been selected for bioassay testing as part of the National Toxicology Program—Carcinogenicity Testing Program (Ref. 1). The selection of a chemical for bioassay does not necessarily imply that it is a carcinogen. Chemicals are selected on the basis of human exposure, production levels, and chemical structure. Selection of a chemical for carcinogenicity testing is not a sufficient basis for withholding conclusions on its effectiveness and on other aspects of safety in an OTC drug final monograph. The inclusion of an ingredient in a final monograph means that the agency has concluded that it is generally recognized as safe and effective based on the evidence available at that time; it does not preclude the possibility that future evidence may demonstrate an ingredient to be unsafe for OTC use. If future evidence, e.g., results of bioassay testing, demonstrates that an ingredient is unsafe for OTC use, the agency will take immediate steps to remove products containing this ingredient from the marketplace.

The Panel had placed the antihistamine methapyrilene in Category III in its report (40 FR 57292 at 57309). In its proposed regulation for OTC nighttime sleep-aid drug products, the agency proposed to place methapyrilene in Category II because of preliminary studies implicating this drug as a carcinogen, or a carcinogen synergist with nitrates, in rats. However, at that time, the studies were too preliminary to support a definitive finding that methapyrilene was itself a carcinogen and had to be removed immediately from all products in the OTC drug market.

Subsequent to the agency's proposed regulation, a National Cancer Institute (NCI) study, not available to the Panel, provided data from which the agency concluded that methapyrilene is a potent carcinogen in animals and must be considered a potential human carcinogen. These data are on file in the Dockets Management Branch (address above) under Docket No. 75N-0244 and have since been published (Ref. 2).

In 1979, in response to an agency-requested recall, all oral and topical products containing methapyrilene were removed from the market. Products containing methapyrilene are now considered to be misbranded under section 502 of the act (21 U.S.C. 352) and "new drugs" under section 201(p) of the act (21 U.S.C. 321(p)). In this document the agency concludes that methapyrilene fumarate and methapyrilene hydrochloride are nonmonograph ingredients.

References

(1) Copy of a computer printout from the National Toxicology Program—Carcinogenicity Testing Program, OTC Volume 050FM, Docket No. 75N-0244, Dockets Management Branch.

(2) Lijinsky, W., M.D. Reuber, and B.N. Blackwell, "Liver Tumors Induced in Rats by Chronic Oral Administration of the Common Antihistamine Methapyrilene Hydrochloride," *Science*, 209:817-819, 1980.

5. One comment requested that FDA require long-term anticholinergic toxicity studies on the Category III nighttime sleep-aid ingredients that are now restricted to prescription use before allowing them on the OTC market. In addition, the comment requested that pyrilamine be removed from the OTC market until such studies are done. The comment was concerned that even though anticholinergic (drying) side effects have been considered negligible in the past, they may be rooted in irreversible tissue damage and neuropharmacologic damage.

Diphenhydramine is the only ingredient currently included in this monograph, and the anticholinergic effects of this drug are well known (Ref. 1). Because diphenhydramine has been safely used for many years and FDA is not aware of any data that indicate that long-term use of this drug can cause irreversible tissue damage and neuropharmacologic damage, the agency finds no need for long-term anticholinergic toxicity studies as requested by the comment. The agency will assess the need for such studies for other ingredients should any other prescription drugs be considered for inclusion in the monograph.

Pyrilamine maleate, presently marketed OTC in a few products as a nighttime sleep-aid, is not included in this final monograph because of a lack of general recognition of effectiveness. (See comment 21 below.) Upon the effective date of the monograph, OTC drug products containing pyrilamine maleate intended for use as a nighttime sleep-aid may not be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved NDA or have been included in the final monograph by that date. The agency does not believe that there is a health hazard associated with this drug so as to require its immediate removal from the market. The agency is aware that a number of OTC nighttime sleep-aid drug products that previously contained pyrilamine maleate have been reformulated to contain diphenhydramine and further expects that the remaining drug products containing pyrilamine maleate will be reformulated with diphenhydramine in advance of the effective date of this final monograph.

Reference

(1) Copy of FDA-approved labeling from NDA 5-845, OTC Volume 050FM, Docket No. 75N-0244, Dockets Management Branch.

6. One comment urged FDA to undertake studies on l-tryptophan, a naturally occurring food substance, as a nighttime sleep-aid. The comment stated that, considering that there is no sleep-aid ingredient that is safe and effective and because drug companies will not spend money for testing substances that cannot be patented, FDA should

undertake such studies for the public good.

The agency appreciates the comment's concerns. However, FDA's primary charge is to ensure that drugs in the marketplace are both safe and effective for their intended use, not to conduct original research in the development of new drugs. In addition, this final monograph contains ingredients that are considered safe and effective for use as OTC nighttime sleep-aids.

7. One comment urged the agency to recognize the legal status of the monographs issued under the OTC drug review as being interpretative rather than substantive regulations.

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drugs published in the **Federal Register** of May 11, 1972 (37 FR 9464), and in paragraph 3 of the preamble to the tentative final monograph for OTC antacid drug products published in the **Federal Register** of November 12, 1973 (38 FR 31260). 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 Association* v. *Weinberger*, 512 F.2d 688, 696–98 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers* v. *FDA*, 437 F. Supp. 412 (S.D.N.Y. 1980), *aff'd*, 637 F.2d 887 (2d Cir. 1981).)

8. One comment disagreed with the agency's statement in the tentative final monograph that the Panel had gone beyond its charter in making statements on advertising (43 FR 25544 at 25545). The comment believed that the agency's statement was in contradiction to a later statement that the OTC advisory review panels "are free to comment, on any scientific or policy issue that they have considered in the course of their review" (43 FR 25558). The comment urged the agency to adopt a formal statement of policy with respect to advertising and include it in the monograph.

The agency disagrees with the comment that the two statements are in contradiction. The OTC advisory review panels were charged to advise the agency on the safety, effectiveness, and labeling of OTC drug products. They were not charged with making recommendations on advertising because the Federal Trade Commission (FTC), not FDA, is the agency that has the primary responsibility for regulating OTC drug advertising. FDA has the authority to regulate OTC drug advertising that constitutes labeling under the Federal Food, Drug, and Cosmetic Act. See, e.g., *United States* v. *Article of Drug * * * B-Complex Cholinos Capsules*, 362 F.2d 923 (3d Cir. 1966); *V.E. Irons, Inc.* v. *United States*, 244 F.2d 34 (10th Cir.); *cert. denied*, 354 U.S. 923 (1957). In addition, for an OTC drug to be generally recognized as safe and effective and not misbranded, the advertising for the drug must, satisfy the FDA regulations in § 330.1(d) (21 CFR 330.1(d)), which state that the advertising may prescribe, recommend, or suggest the drug's use only under the conditions stated in the labeling. If advertising for an OTC nighttime sleep-aid drug product offers the product for conditions not included in the final monograph labeling, the drug product may be subject to regulatory action by FDA. Therefore, as stated in the tentative final monograph, advisory review panels are free to comment on any aspect of OTC drug regulation notwithstanding FDA's limited authority to implement their recommendations. Because the agency's jurisdiction over OTC drug advertising is already stated in the act and in existing agency regulations that are applicable to all OTC drug monographs, the comment's request for inclusion of a policy statement on advertising in this particular monograph is not necessary.

9. One comment disagreed with the agency's statements in the tentative final monograph that the Consumer Product Safety Commission (CPSC) and not FDA has the authority to place limitations on package size (43 FR 25544 at 25546). The comment stated that CPSC has authority to require child-resistant closures, but does not have the authority to regulate the quantity available in a product container. The comment expressed the belief that, under the act, FDA has authority to limit the conditions under which a drug is used including the quantity of drug in a container. Because of the Panel's concern for potential harm to children if large quantities of any nighttime sleep-aid are ingested, the comment requested that the agency restrict the quantity of a nighttime sleep-aid packaged per container to a safe level or include a warning that ingestion of large quantities could be lethal. The comment also requested a hearing on this issue.

The agency agrees with the comment that FDA does have authority to place limitations on package size when deemed necessary, e.g., the recommended limitations in the quantity of 1¼ grain (pediatric) aspirin tablets to 36 tablets per container (21 CFR 201.314(c)). Concerning the comment's request that the agency restrict the amount of drug in a nighttime sleep-aid container, however, no evidence has been presented to warrant such a restriction.

CPSC has the authority to require child-resistant closures. FDA is aware that CPSC has reviewed the available data on antihistamines and has determined that child-resistant closures are warranted for OTC drug products, including nighttime sleep-aids, containing more than 66 milligrams (mg) diphenhydramine base in any oral dosage form. (See 16 CFR 1700.14(a)(17).) The comment did not submit any data that indicate a need to limit the package size of OTC nighttime sleep-aid drug products containing diphenhydramine nor did it submit any data that indicate a need to include a warning that ingestion of large quantities could be lethal. Therefore, FDA does not believe that limiting the package size for OTC diphenhydramine-containing nighttime sleep-aids or a warning is necessary at this time. If the agency proposed limiting the package size of such drug products to 66 mg diphenhydramine or less, each package would contain only one adult dose of 50 mg. Limiting the package size to a single dose would be impractical. In view of CPSC's final rule on child-resistant packaging, the impracticality of limiting a package size to a single dose, and the comment's failure to submit data supporting the need for further action, the Commissioner concludes that a hearing by FDA on this issue is not warranted at this time.

10. One comment requested FDA to join with FTC in conducting hearings on the possibilities of deception in labeling and advertising caused by "look-alike/sound-alike" drugs. The comment noted that the agency's response to this issue was that if "look-alike/sound-alike" drugs presented an opportunity for abuse, appropriate action would be initiated under section 502(a) of the act (see comment 19, 43 FR 25544 at 25547). The comment maintained "that enough evidence is present to warrant affirmative action on this issue."

The agency recognizes the potential for deception in the marketing of OTC "look-alike/sound-alike" drugs, including certain OTC nighttime sleep-aids that bear a strong physical resemblance to certain controlled prescription drugs, or have trade names that sound like those of controlled drugs. Since publication of the tentative final monograph, the agency has become aware that there is widespread manufacturing, promotion, and marketing of these OTC "look-alikes." The agency has initiated seizure actions under the counterfeit drug sections of the act (sections 201(g)(2) and 304(a)(2)), separate from the OTC drug review, in

order to remove these products from the market. Moreover, there have been several Congressional hearings on this subject in recent years, and the agency has also discussed this issue in other **Federal Register** documents. (See New Drug Status of OTC Combination Drug Products Containing Caffeine, Phenylpropanolamine, and Ephedrine, published in the **Federal Register** of August 13, 1982 (47 FR 35344); Enforcement Action for Certain OTC Drug Products, published in the **Federal Register** of November 18, 1983 (48 FR 52513); and Enforcement Action Under the New Drug Provisions of the Federal Food, Drug, and Cosmetic Act; Certain OTC Drug Products; Advisory Opinion; Amendment, published in the **Federal Register** of June 29, 1984 (49 FR 26814).) This issue is also discussed with respect to diphenhydramine in comment 22 below. Based on previous agency actions and the Congressional hearings that have already been held, the agency concludes that an additional joint hearing with the FTC to discuss labeling and advertising for such products is not needed.

B. Comments on Labeling of OTC Nighttime Sleep-Aid Drug Products

11. Several comments contended that FDA does not have the authority to legislate the exact wording of OTC labeling claims. The comments contended that such a policy is overly restrictive, lacks supporting evidence, and constitutes a prior restraint on First Amendment rights. The comments concluded that to ban alternative truthful language is unjustified. Two comments also requested a hearing on this issue.

In the **Federal Register** of May 1, 1986 (51 FR 16258), the agency published a final rule changing its labeling policy for stating the indications for use of OTC drug products. Under 21 CFR 330.1(c)(2), the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either (1) the specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "APPROVED USES"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "APPROVED USES"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "APPROVED USES," plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All other OTC drug labeling required by a monograph or other regulation (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under the OTC drug monograph or other regulation where exact language has been established and identified by quotation marks, e.g., 21 CFR 201.63 or 330.1(g). The final rule in this document is subject to the labeling provisions in § 330.1(c)(2).

12. One comment objected to the agency's conclusion in comment 45 of the tentative final monograph (43 FR 25544 at 25553) that the claim "reduced time to fall asleep" is not synonymous with the Category I claim "helps fall asleep" and contended that the only reason for denying the reduced time claim was that such a phrase would suggest that someone without a sleep disturbance could use a sleep-aid. The comment requested a hearing on this issue.

In the tentative final monograph, the agency determined that the claim "reduced time to fall asleep" was not fully synonymous with the requirements for Category I nighttime sleep-aid ingredients. The agency stated that the use of a nighttime sleep-aid should reduce the time required for a person to get to sleep by providing the means for such sleep in the case of an individual who might otherwise remain awake. The agency concluded that the unqualified claim "reduced time to fall asleep" required further study because it implies that persons without sleep disturbances may benefit from the use of OTC nighttime sleep-aids, and no such data had been presented. However, in patients with insomnia (difficulty falling asleep), such a claim would be reasonable. At the time that the tentative final monograph was proposed (1978), there were no Category I nighttime sleep-aid ingredients. Based on the panel's recommendations (40 FR 57292 at 57328), the agency proposed as one of the suggested phrases the claim "helps fall asleep," but stated that additional studies would be necessary to support such a claim. Subsequently, studies were submitted to upgrade Category III ingredients to monograph status. The studies that were found acceptable (see comment 22 below) were conducted in persons with sleep difficulties. In those studies, sleep latency (time to fall asleep) was a major parameter studied, and those ingredients found to be effective as OTC nighttime sleep-aids were able to reduce the time to fall asleep. Accordingly, the claim "reduced time to fall asleep" has been substantiated, but only in individuals with occasional sleeplessness or who have difficulty falling asleep. Therefore, the agency is adding the claim ("Helps you" or "Reduces time to") "fall asleep if you have difficulty falling asleep" to the indications section of the monograph.

Based upon these studies, the unqualified claims "reduces time to fall asleep" and the previously proposed "helps fall asleep" without the descriptive language relating these claims to the intended target population are not appropriate as specific indications for OTC nighttime sleep-aid drug products. However, because the phrases "helps fall asleep" and "reduces time to fall asleep" are part of the monograph indications for nighttime sleep-aid drug products, the agency would not object to these shortened phrases appearing elsewhere in the labeling (i.e., outside the boxed area), provided that the complete indication statement(s) appears in the appropriate place in the labeling.

Based upon the discussion above, the agency has revised the definition of a nighttime sleep-aid that appears in this final monograph to read as follows: "A drug that is useful for the relief of occasional sleeplessness by individuals who have difficulty falling asleep." Likewise, the indications have been revised to (1) ("Helps you" or "Reduces time to") "fall asleep if you have difficulty falling asleep," (2) "For relief of occasional sleeplessness," and (3) "Helps to reduce difficulty falling asleep." The agency concludes that these changes make it clear that OTC nighttime sleep-aids are intended only for those individuals who have occasional sleeplessness or who have difficulty falling asleep. Based on these changes, the Commissioner concludes that a hearing on this issue is not warranted.

13. One comment objected to the Category II classification of the terms "refreshing sleep" and "sound sleep." The comment argued that the person who uses an OTC nighttime sleep-aid wants to avoid occasional sleeplessness and desires sleep that is refreshing. For this reason, the comment requested that the term "refreshing sleep" as well as the terms "restful sleep" and "good night's sleep" be moved to Category I. Regarding the term "sound sleep," the comment claimed that a person who experiences "sound sleep" experiences a sleep with fewer awakenings. The comment argued that for this reason the "sound sleep" claim and the "fewer awakenings" claim should be placed in the same category. The comment noted that the "fewer awakenings" claim was placed in Category III in the tentative

final monograph, but urged that this claim and the "sound sleep" claim both be included in the monograph. The comment also requested a hearing on this issue.

Another comment objected to the agency's Category II placement of the claim "helps you relax so you can fall asleep." Arguing that the agency conceded that nighttime sleep-aids provide a relaxant action, the comment referred to the agency's statement at 43 FR 25553 that such a "product will make one drowsy, not just relaxed * * *." The comment requested that this claim be moved from Category II to Category I.

The above classifications were made in the tentative final monograph before the agency received the results of any clinical studies that supported monograph status for any OTC nighttime sleep-aid drug. Since that time, the agency has evaluated the results of clinical studies that support the safety and effectiveness of diphenhydramine hydrochloride and diphenhydramine citrate for nighttime sleep-aid use. (See comment 22 below.)

In those studies, a number of efficacy variables related to the claims and terms requested by the comments were evaluated. These included the following: (1) How much did the medication help?, (2) wake time, (3) how rested when woke?, (4) how sleepy during day?, (5) how energetic during day?, (6) sleep latency, (7) number of awakenings, (8) sleep duration, (9) depth of sleep, and (10) how good was the sleep?

As discussed in comment 22 below, in one study, diphenhydramine hydrochloride was significantly better ($p=.05$) than placebo for sleep latency, degree to which medication helped, depth of sleep, and quality (goodness) of sleep. At the less conservative .10 level of significance, diphenhydramine was better than placebo for the amount of time spent awake in bed. In another study, diphenhydramine was significantly better ($p=.05$) than placebo for sleep latency, degree to which medication helped, depth of sleep, quality (goodness) of sleep, feeling rested upon awakening, and degree of energy during previous day. At the less conservative .10 level of significance, diphenhydramine was better than placebo for the amount of time spent awake in bed. All other variables evaluated in the studies were not significant.

The claim relating to fewer awakenings, which was placed in Category III in the tentative final monograph, reads as follows: "Reduces the number of awakenings in persons who wake frequently during the night" (43 FR 25544 at 25588). The agency concluded that this would be a valid claim for OTC nighttime sleep-aids if supported by evidence in well-controlled studies. However, none of the studies submitted to support the effectiveness of diphenhydramine as an OTC nighttime sleep-aid supports that claim. Therefore, the scientific data are inadequate to allow inclusion of the "fewer awakenings" claim in the monograph.

Based on the results of the diphenhydramine studies, which showed that the nighttime sleep-aid drug improved depth of sleep, quality (goodness) of sleep, feeling rested upon awakening, and degree of energy during previous day, the agency concludes that the data support the terms "sound sleep," "restful sleep," "good night's sleep," and "refreshing sleep" for nighttime sleep-aid drug products. Further, the agency notes that the concept of rest is included in at least two dictionary definitions for "relax" (Refs. 1 and 2); therefore, the term "relaxing" sleep is also acceptable. However, the agency considers these terms to be descriptive statements that do not relate in a significant way to the safe and effective use of nighttime sleep-aid drug products and, therefore, does not consider such information to be necessary as part of the required indications for these products. Because these terms are examples of truthful and nonmisleading language, the agency would allow the terms to be included in labeling provided they are not intermixed with labeling established by the monograph. Based on the above discussion, the Commissioner concludes that a hearing on this issue is not warranted.

Regarding the statement (made by the agency in the tentative final monograph at 43 FR 25544 at 25553) referred to by the comment, the agency was not conceding that OTC nighttime sleep-aids act by relaxing, but rather intended to emphasize that these drugs act by making one drowsy. Regarding the claim "helps you relax so you can fall asleep," the agency considers such a claim as relating to the mechanism of action of the drug. This efficacy variable was not evaluated as part of the diphenhydramine studies. Therefore, because the data are inadequate to support such a claim, it is not being included in the monograph.

References

(1) "Webster's Collegiate Dictionary," G. and C. Merriam Co., Springfield, MA, 1976, s.v. "relaxing."

(2) "The American Heritage Dictionary of the English Language," Houghton Mifflin Co., Boston, 1976, s.v. "relaxing."

14. One comment objected to the warning in proposed § 338.50(c)(2): "If condition persists continuously for more than 2 weeks, consult your physician. Insomnia may be a symptom of serious underlying medical illness." The comment referred to reasoning provided in its earlier comment to the Panel's report that there is insufficient evidence of abuse of OTC nighttime sleep-aid drug products to warrant such a warning.

In addressing this issue in comment 51 of the tentative final monograph (43 FR 25544 at 25554), the agency tentatively concluded that the warning was necessary because it would help the user to determine when the limits of self-treatment have been reached. The present comment offers no basis to alter the agency's conclusions; therefore, the warning is included in the final monograph.

15. Several comments objected to the glaucoma warning proposed in § 338.50(c)(3)(i). One comment stated that incorporation of this warning, based on a recommendation of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products, fails to recognize the difference between the dosage and pattern of use of antihistamines in OTC nighttime sleep-aid products and antihistamines in cough/cold products. The comment also cited testimony that a particular sleep-aid drug product containing methapyrilene and scopolamine is safe when administered to patients with glaucoma (Ref. 1).

The agency recognizes that antihistamines used as OTC nighttime sleep-aids are taken only once a day, whereas they may be taken up to six times a day for cough/cold symptoms. However, the nighttime sleep-aid dosage is often higher than the cough/cold dosage. In addition, there is variation between the different antihistamine drugs with respect to the degree of expected side effects, and also marked individual variation in response to antihistamine drugs (Ref. 2). Thus, the agency believes it best to advise consumers with glaucoma to seek the advice of a physician before using antihistamine-containing OTC drug products. The warning, therefore, has been retained in the OTC nighttime sleep-aid final monograph. The comment's cited testimony does not support deleting this warning because neither methapyrilene nor scopolamine

are included in the OTC nighttime sleep-aid final monograph.

References

(1) Comment No. HER003, Docket No. 75N-0244, Dockets Management Branch.

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

16. Several comments objected to the proposed alcohol-antihistamine drug interaction warning in § 338.50(c)(3)(ii), which reads "Take this product with caution if alcohol is being consumed." One comment stated that the agency did not provide documentation for a potential hazard, and without such documentation it is inappropriate to require such a warning.

The agency disagrees with the comments. In the tentative final monograph, the agency noted that the Sleep-aid Panel had documentation at 40 FR 57308 of an alcohol-antihistamine interaction in which deepened and prolonged sleep was reported. (See 43 FR 25544 at 25554.) The agency concluded that the depressant effects of antihistamines and alcohol are additive and could create a greater soporific effect than is desirable (43 FR 25566). In addition to the reference cited by the Panel at 40 FR 57308, the agency points out that the additive central nervous system depression occurring from simultaneous ingestion of antihistamines and alcohol is well-documented in the literature (Refs. 1 through 5).

In the tentative final monograph for OTC nighttime sleep-aid drug products, the agency also noted that the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products had recommended an antihistamine-alcohol drug interaction warning (43 FR 25544 at 25554). In an amendment to the tentative final monograph for OTC antihistamine drug products, published in the **Federal Register** of August 24, 1987 (52 FR 31892), the agency noted that, in addition to alcohol, sedative and tranquilizer drugs are known to have additive effects to the drowsiness effect of antihistamine drug products (52 FR 31911). The agency stated that it felt that consumers should be warned about these additive effects and proposed a revision to the warnings for OTC antihistamine drug products, which read as follows: "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 has reviewed the comments received in response to the publication of that proposed warning. No comments in opposition to that revised warning were received.

Besides alcohol, the Sleep-aid Panel also stated that the depressant actions of antihistamines are additive with the effects of other central nervous system depressants and the concomitant use of * * * drugs known to depress the central nervous system should be avoided because such combinations produce deepened and prolonged sleep (40 FR 57292 at 57308) and excessive sedation and confusion (40 FR 57297).

The agency concludes that this important information should appear in the labeling of OTC nighttime sleep-aid drug products to provide for the safe consumer use of these products. However, because of the intended use of a nighttime sleep-aid drug product, the information should be different from that appearing on antihistamine drug products for daytime cold or anti-allergy use. For those products, the drowsiness or marked drowsiness caused by the antihistamine is a side effect that consumers need to be alerted to, and consumers should be informed to use caution when driving a motor vehicle or operating machinery. Because the "Directions" for a nighttime sleep-aid drug product are for use at bedtime, or as directed by a doctor, it is not necessary to include a warning against use while driving a motor vehicle or operating machinery. However, the potential of excessive sedation or confusion (as noted above) exists if the sleep-aid product is taken concomitantly with alcohol, sedatives, or tranquilizers. Therefore, the agency is including the following warning in this final monograph: "Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor."

References

(1) Noble, E.P., "Third Special Report to the U.S. Congress on Alcohol and Health," Department of Health, Education, and Welfare, National Institute on Alcohol Abuse and Alcoholism, Rockville, MD, p. 50, June 1978.

(2) "British Pharmaceutical Codex 1963," Council of the Pharmaceutical Society of Great Britain, The Pharmaceutical Press, London, p. 20, 1963.

(3) McIver, A.K., "Drug Incompatibilities," *The Pharmaceutical Journal*, 195:609-612, 1965.

(4) "Interactions of Alcohol with Drugs," *The Medical Letter*, 19:48, 1977.

(5) Coleman, J.H., and W.E. Evans, "Drug Interactions with Alcohol," *Alcohol Health and Research World*, Department of Health, Education, and Welfare, National Institute on Alcohol Abuse and Alcoholism, Rockville, MD, pp. 16-19, 1975.

17. Several comments urged the agency to reconsider the need for inclusion of a warning on the label of OTC nighttime sleep-aid drug products regarding the use of these drugs by pregnant or nursing women. The comments contended that even though there are no data to suggest a potential hazard, there have been no studies to show that these drugs are safe when taken by pregnant or nursing women and that a warning regarding the use of these drugs by pregnant and nursing women should be included in the monograph.

In the **Federal Register** of December 3, 1982 (47 FR 54750), the agency published a final rule requiring that the labeling for all OTC drugs that are intended for systemic absorption, unless specifically exempted, contain a general warning concerning the use of these drugs by pregnant or nursing women. This warning states: "As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product." The regulation provides that if a specific warning relating to use during pregnancy or while nursing has been established for a particular drug product in an NDA or for a product covered by an OTC drug final monograph in Part 330, the specific warning shall be used in place of the general pregnancy-nursing warning unless otherwise stated in the NDA or in the final OTC drug monograph. The agency is not aware of any data at this time that would necessitate a special warning for the active ingredients included in the OTC nighttime sleep-aid final monograph. Therefore, these drug products will be required to bear the general pregnancy-nursing warning in § 201.63, as stated above.

18. One comment objected to the monograph limitation of a single dose of a nighttime sleep-aid at bedtime because there is no factual evidence that would indicate that a repeat dose in 4 hours is not safe and effective. The comment requested that the monograph be amended to include the provision for a repeat dose in 4 hours if necessary.

The agency recognizes that an antihistamine that is marketed OTC for relief of cough/cold symptoms bears directions for use that recommend a repeat dose every 4 hours as needed.

Although the comment is correct that there is no evidence to show that repeating the OTC nighttime sleep-aid dose would not be safe and effective, data on a repeat dose in 4 hours were not submitted to the agency and the comment presented none. In addition, the data that were submitted demonstrated that the antihistamines are an effective sleep-aid after only one dose has been taken. Therefore, the directions for use in this final rule have not been revised to include a repeat dose.

19. One comment recommended that the agency adopt a "Labeling General Statement" in the final monograph to explain FDA's position on the following aspects of OTC drug labeling: Confusing claims, unsupported or misleading claims, claims implying a unique action, statement of quantity of active ingredients, declaration of inactive ingredients, and general warning statements.

The agency believes that the OTC drug regulations in Part 330 explain the agency's policy regarding many of the items outlined by the comment. For example, § 330.1(e) explains the position regarding inactive ingredients in OTC drug products; § 330.1(g) contains general warning statements that should be included on all OTC drug products (see also discussion of the general pregnancy-nursing warning in comment 7 above); § 330.1(j) recommends that the labeling contain the quantitative amounts of active ingredient per dosage unit; and § 330.10(a)(4)(v) states that "labeling shall be clear and truthful in all respects and may not be false or misleading in any particular." Specific labeling claims or problems are adequately discussed in the respective rulemakings. In light of the discussion above, the agency does not believe it is necessary to adopt a general labeling statement as recommended by the comment.

C. Comments on Combination Drug Products

20. One comment disagreed with the agency's conclusions regarding combinations of OTC nighttime sleep-aids with analgesic ingredients. Specifically, the comment objected to the agency's insistence on factorially designed studies to demonstrate a target population that would benefit from such combinations. The comment contended that there is compelling logic for the existence of a target population of individuals with sleeplessness due to pain and that the tension component of pain produces a degree of sleeplessness beyond that produced by the pain itself. Although an analgesic may relieve the pain and indirectly relieve the tension and allow for sleep, the nighttime sleep-aid ingredient will enhance this effect by directly relieving the tension and its resultant sleeplessness. The comment referred to a published article to support this theory (Ref. 1).

The comment further argued that the OTC drug regulations in § 330.10(a)(4)(iv) do not require a showing that each ingredient in a combination product is needed. The comment pointed out that the regulations for prescription drug combination products (21 CFR 300.50) make it mandatory not only that each ingredient make a contribution, "but also that there be a significant patient population requiring such concurrent therapy." The comment stated that the absence of such specific language in the OTC drug regulations makes it clear that, for OTC drug combinations, each ingredient does not have to be shown to be needed.

Several comments submitted results of a number of studies in which nighttime sleep-aid/analgesic combination drug products were evaluated to determine whether such combinations should be generally recognized as safe and effective in the final monograph (Ref. 2). One comment also requested a hearing on this issue.

The article cited by the comment (Ref. 1) does not support the claimed theory that the addition of an antihistamine to an analgesic, for use in individuals with sleeplessness due to pain, provides for relief of the tension component of pain and its resultant sleeplessness. In this randomized, double-blind, crossover study, 206 patients were treated for "simple nervous tension accompanied by headache" using phenyltoloxamine citrate alone, acetaminophen alone, the combination of these two drugs, or placebo. The subjects rated each treatment with respect to degree of relief and time interval until maximum relief was obtained for each of the symptoms of tension, anxiety, irritability, and headache. Sleep was not a measured parameter in this study and, therefore, the study is of little value in assessing the effectiveness of the antihistamine in providing or enhancing a sleep effect.

The agency has also reviewed the clinical studies and information submitted in the other comments (Ref. 2). These studies contain new data on the safety and effectiveness of a combination of two analgesics with diphenhydramine for use as a nighttime pain reliever. These studies, however, "do not provide comparisons between the combinations and their individual antihistamine and analgesic components" (Ref. 3). The agency concludes that the available data remain insufficient to demonstrate whether the addition of a nighttime sleep-aid enhances the effectiveness of the analgesic to allow labeling the product as a "nighttime pain reliever."

Regarding the need to identify a target population that could benefit from an OTC nighttime pain reliever, the agency recognizes the fact that the study design proposed in the OTC nighttime sleep-aid tentative final monograph separated the test population into two groups, i.e., individuals with sleeplessness related to pain and those who suffer from sleeplessness not related to pain. In proposing this latter group, the agency recognized the existence of a suitable target population for the combination of an OTC nighttime sleep-aid and internal analgesic(s). In this patient population are individuals who might on a given night have both sleep problems and mild to moderate pain. In cases where only one symptom occurs, it is more appropriate to select drugs separately for specific symptomatic relief.

Since publication of the Panel's findings and the tentative final monograph, the agency announced on November 28, 1978, the availability of a guideline that states in detail its policy for combining two or more safe and effective OTC active drug ingredients (43 FR 55466). The agency uses this guideline in addition to the existing regulatory requirements for OTC combination drugs in § 330.10(a)(4)(iv). The guideline is currently available for public examination at FDA's Dockets Management Branch (Docket No. 78D-0322). Item (1) of the guidelines states, "Category I active ingredients from different therapeutic categories may be combined to treat different symptoms concurrently only if each ingredient is present within its established safe and effective dosage range and the combination meets the OTC combination policy in all other respects."

In reviewing the information available several years ago, the agency tentatively concluded that the combination of an OTC nighttime sleep-aid and OTC internal analgesic(s) was reasonable, provided the combination was properly labeled for use only when concurrent symptoms exist, e.g., for occasional minor aches, pains, and headache with accompanying sleeplessness. Accordingly, at that time, the agency planned to reclassify the combination of a nighttime sleep-aid and internal analgesic(s) from Category III to Category I.

The agency's detailed comments and evaluation of the data are on file in the Dockets Management Branch (Ref. 4).

Subsequently, the agency reevaluated the existing information and has tentatively concluded that the combination of an OTC nighttime sleep-aid and OTC internal analgesic(s) should not be included in the final monograph at this time. Even though the agency had earlier indicated that one can reasonably conclude that an appropriate patient population exists, i.e., patients with pain with concurrent sleeplessness unrelated to the pain, the agency now believes that a more scientific basis is needed to support this conclusion. The agency believes that it must be shown with valid data that there is a population needing a product identified as an "analgesic/nighttime sleep-aid." The agency also believes that data are needed to show that the sleeplessness is not relieved by the analgesic alone but that both ingredients in the combination product contribute to its claimed effects. A study is needed in which the contribution of both components has been shown to relieve the sleeplessness. The agency believes that the best study population for this purpose would be one in which patients complain of sleeplessness that is not perceived as resulting from the pain they have. If a target population with concomitant pain and sleeplessness that clearly requires both an analgesic and a nighttime sleep-aid can be established, then labeling for such a combination would have to state clearly that it is for use only when both symptoms occur together, not when only one occurs and/or the other is anticipated.

The agency's detailed comments and reevaluation of the data are on file in the Dockets Management Branch (Ref. 5). In response to the agency's letter, additional data containing the results of two factorial design clinical studies were submitted to the agency on December 22, 1986 (Ref. 6). The data are presently under review.

In view of the change in the agency's tentative conclusions on the data (Refs. 4 and 5) and the submission of additional data, and because a hearing was requested on this combination issue, the agency is not issuing a final decision on the appropriateness of a combination of an OTC nighttime sleep-aid and an OTC internal analgesic(s) at this time. A final decision on this issue will be published in a future issue of the **Federal Register**. Prior to any final agency action, an opportunity for a hearing on this issue will be provided unless the comment advises the agency otherwise. An appropriate notice will be published in the **Federal Register**.

The agency has determined that because all issues relating to single-ingredient nighttime sleep-aid drug products have been resolved, a final monograph covering only these products should be issued before the status of the combination is resolved. Accordingly, combinations of a monograph nighttime sleep-aid and an internal analgesic(s) are exempt from the requirements of the final rule until a final decision on such a combination is issued in a future issue of the **Federal Register**.

References

(1) Gilbert, M. M., N. De Sola Pool, and C. Schecter, "Analgesic/Calmative Effects of Acetaminophen and Phenyltoloxamine In Treatment of Simple Nervous Tension Accompanied By Headache," *Current Therapeutic Research*, 20:53–58, 1976.

(2) Comment Nos. OB0018, C00031, and C00032, Docket No. 75N–0244, Dockets Management Branch.

(3) Letter from W. E. Gilbertson, FDA, to B. M. Lanman, Bristol Myers Products. coded LET003, Docket No. 75N–0244, Dockets Management Branch.

(4) Letter from W. E. Gilbertson, FDA, to W. B. Elvers, Bristol Myers Products, coded LET009, Docket No. 75N–0244, Dockets Management Branch.

(5) Letter from W. E. Gilbertson, FDA, to W. B. Elvers, Bristol Myers Products coded LET012, Docket No. 75N–0244, Dockets Management Branch.

(6) Comment No. C00038, Docket No. 75N–0244, Dockets Management Branch.

D. Comments on Pyrilamine

21. Results of several studies were submitted to support general recognition of the safety and effectiveness of pyrilamine maleate as an OTC nighttime sleep-aid ingredient (Refs. 1 through 4). One comment recommended removing pyrilamine from the OTC market as a nighttime sleep-aid ingredient because long-term carcinogenicity studies have not been performed and because anorexia, nausea, and vomiting are commonly encountered when doses of 25 to 50 mg are ingested (43 FR 25544 at 25588).

The data submitted by the comments included a clinical study by Fabre (Ref. 2); a clinical study by Hartmann, Marsh, and Soderland (Ref. 3); and a sleep laboratory study by Vogel (Ref. 4). The agency has reviewed these studies and concludes that they do not support the reclassification of pyrilamine maleate from Category III to Category I as an OTC nighttime sleep-aid.

Fabre study (Ref. 2). This study was a randomized, double-blind, two-treatment, two-period crossover study conducted at two different sites (Houston and Austin) comparing 50 mg pyrilamine maleate to placebo in 100 patients with mild, nonchronic insomnia. Each treatment period lasted 1 week and there was no washout between periods.

Considering the data as analyzed, the accuracy of the signed-rank tests are difficult to verify because the analyses are poorly documented. Instead of presenting the sum of the ranks, the mean of the ranks was used. The test procedure is based on the sum, and the mean is irrelevant and uninformative. Even ignoring the problems with the data analyses, the results are very unusual. Every comparison was highly significant ($p=0.005$) in favor of pyrilamine in the Houston clinic. Only one variable, sleep duration, was significant ($p=0.02$) in favor of pyrilamine in the Austin clinic. For the remaining variables, the smallest significance level was $p=0.12$. There are no apparent reasons for the disparity between the two clinics.

Hartmann, Marsh, and Soderland study (Ref. 3). This study had the same basic design as the Fabre study except that the treatment periods were 6 days long and there was a 2-day washout period between treatments. One-hundred-eight subjects satisfied the selection criteria; one patient was excluded from the analysis. For inclusion into the study, subjects were to have mild, nonchronic difficulties in falling asleep for at least 30 minutes. However, over 50 percent of the subjects reported they usually fell asleep within 15 minutes, thus making efficacy difficult to demonstrate.

Analyses were presented for both the daily sleep questionnaires and the post-treatment questionnaires. However, as with the Fabre study, some analyses were not appropriate for a crossover study, and those that were appropriate were poorly documented. In addition, the roles of the three investigators were not defined. Therefore, the agency is unable to assess whether investigator bias was introduced into the treatment comparisons.

Vogel study (Ref. 4). This was a 10-day, double-blind, sleep laboratory study comparing pyrilamine 50 mg to placebo in 14 subjects with subjective and objective sleep onset insomnia. FDA's nonparametric analyses showed significantly fewer awakenings ($p=0.01$) and significantly shorter wake time after first persistent sleep onset ($p=0.02$) with pyrilamine as compared to baseline. However, there were no significant improvements for total sleep time ($p=0.22$), sleep latency to first sleep ($p=0.13$), and sleep latency to first persistent sleep ($p=0.70$). In fact, the

mean sleep latency to first persistent sleep, the objective variable used as a criterion for entrance into the study, increased with pyrilamine by 18 minutes. Thus, the persistent sleep latency actually worsened with pyrilamine as compared to the placebo baseline nights. For the subjective variables, there were no comparisons that were significant at $p=0.05$.

On April 16, 1982, additional information was submitted to the agency (Ref. 5), including letters from Drs. Fabre, Hartmann, and Vogel addressing the agency's comments and evaluation (Ref. 6) on their studies. In a letter dated April 4, 1983, the agency discussed its review of these letters and concluded that the data provide insufficient evidence of effectiveness for pyrilamine as an OTC nighttime sleep-aid (Ref. 7). In its letter, FDA discussed the following:

(1) There were no analyses of the first period data of the Fabre study (Ref. 2) despite the fact that the lack of such analyses was addressed earlier in the agency's comments and evaluation of June 17, 1981 (Ref. 6). The data submitted are still based on analyses which are not appropriate for crossover studies, and there was no satisfactory explanation for the large disparity between the results of the Austin and Houston clinics. It is difficult to conclude that these differences could be attributed to the demographic differences between the two clinics as suggested by Dr. Fabre.

(2) Of the five efficacy variables (sleep latency, number of awakenings, total time spent awake, sleep duration, and sleep quality) suggested for testing in the Hartmann, Marsh, and Soderland study (Ref. 3), none favor pyrilamine at the 0.05 level of significance. Only two variables (sleep latency and quality of sleep) favor pyrilamine and only at the 0.10 significance level (Ref. 8). The agency has reviewed the new analysis by Dr. Hartmann, which reportedly demonstrates the superiority of pyrilamine compared to placebo at greater statistical significance if subjects with a sleep latency in excess of 15 minutes are analyzed separately. It was necessary to exclude slightly more than half of the patients who could be evaluated in order to show a difference in sleep latency that favored pyrilamine at the 0.05 level of significance. Little weight can be attached to results that were obtained by excluding more than half of the patients on the basis of an apparently arbitrary criterion.

Dr. Hartmann has stated that his patients had mild sleep latency problems, but generally were not suffering from other forms of insomnia. The fact that less than half the patients' usual sleep latency exceeded 15 minutes, and only for 13 percent did it exceed 30 minutes, leads to the conclusion that these patients' sleep latency problems were so mild that the inconclusive results may be attributed to poor patient selection.

(3) The results of the Vogel study (Ref. 4) do not show that pyrilamine reduces sleep latency. Based on the fact that sleep laboratory studies have been able to show an effect on sleep latency for two other OTC nighttime sleep-aids (diphenhydramine and doxylamine), the agency concludes that the results of this study do not support pyrilamine's claim of effectiveness as a nighttime sleep-aid.

Based on the additional information submitted, the agency concludes that the data are still inadequate to include pyrilamine in the monograph (Category I) for use as an OTC nighttime sleep-aid. The agency's detailed comments and evaluation of the additional information are on file in the Dockets Management Branch (Refs. 6, 7, and 8).

References

(1) Comment No. C00031, Docket No. 75N–0244, Dockets Management Branch.

(2) Fabre, L.F., "Double-Blind Controlled Evaluation of Pyrilamine Maleate and Placebo in Insomniac Patients Suffering Primarily From Difficulties Falling Asleep," unpublished study No. I, Comment Nos. C00033 and SUP006, Docket No. 75N–0244, Dockets Management Branch.

(3) Hartmann, E.L., E.B. Marsh, and C.A. Soderland, "The Clinical Evaluation of Pyrilamine Maleate vs. Placebo as a Nighttime Sleep-aid for Patients With Occasional Non-chronic Insomnia," unpublished study No. II, Comment Nos. C00033 and SUP006, Docket No. 75N–0244, Dockets Management Branch.

(4) Vogel, G.W., "The Effects of Pyrilamine Maleate 50 mg on the Sleep Cycle of Healthy Adults with Insomnia," unpublished study No. III, Comment Nos. C00033 and SUP006, Docket No. 75N–0244, Dockets Management Branch.

(5) Letter from A.G. Eckian to W.E. Gilbertson, FDA, coded LET008, Docket No. 75N–0244, Dockets Management Branch.

(6) Letter from W. E. Gilbertson, FDA, to A. G. Eckian, coded LET005, Docket No. 75N–0244, Dockets Management Branch.

(7) Letter from W. E. Gilbertson, FDA, to A. G. Eckian, coded LET011, Docket No. 75N–0244, Dockets Management Branch.

(8) Letter from W. E. Gilbertson, FDA, to A. G. Eckian, coded CR0003, Docket No. 75N–0244, Dockets Management Branch.

E. Comments on Diphenhydramine

22. The results of several studies were submitted to support general recognition of the safety and effectiveness of diphenhydramine hydrochloride and diphenhydramine citrate as OTC nighttime sleep-aid ingredients (Refs. 1 through 12). Diphenhydramine hydrochloride was evaluated in eight studies (Refs. 1 through 8) and diphenhydramine citrate in the other four studies (Refs. 9 through 12).

The agency finds that many of the clinical studies conducted with diphenhydramine hydrochloride (Refs. 1 through 8) were conducted on hospitalized patients and not on the target population, e.g., mild insomniacs, or lacked proper sample size or protocol design and therefore are supportive of effectiveness, but do not alone establish general recognition of OTC safety and effectiveness. For example, one double-blind placebo-controlled study (Ref. 5) compared the effects of 50 mg and 100 mg diphenhydramine hydrochloride in 584 post-ophthalmic surgery patients at the Massachusetts Eye and Ear Infirmary who anticipated having trouble sleeping. The duration of therapy was one night. Side effects were also measured and grouped into eight categories. Both the 50 mg and 100 mg doses of diphenhydramine hydrochloride were significantly superior to placebo. The differences in efficacy between the 50 mg and 100 mg doses were not statistically significant although the incidence of anticholinergic side effects was significantly higher in the 100-mg group. The incidence of other side effects was low with no significant differences between the two drug groups and the placebo group. This study is acceptable as evidence of the hypnotic efficacy and safety of diphenhydramine hydrochloride. The study establishes the optimal dose of diphenhydramine hydrochloride as 50 mg because the 100-mg dose was associated with a significant increase in anticholinergic side effects with no added increase in effectiveness.

The studies by Rickels (Ref. 6) and Finnerty and Goldberg (Ref. 7), conducted in Philadelphia and Boston, support the effectiveness of diphenhydramine as a nighttime sleep-aid. These studies were randomized, double-blind, two-treatment, two-period crossover studies with each period lasting 1 week. Both studies compared 50 mg diphenhydramine hydrochloride to placebo in healthy adults who had mild nonchronic insomnia.

In the Philadelphia study, diphenhydramine hydrochloride was significantly better ($p=0.05$) than placebo for sleep latency, degree to which medication helped, depth of sleep, and quality of sleep. At the less conservative 0.10 level of significance, diphenhydramine was better than placebo for the amount of time spent awake in bed.

In the Boston study, diphenhydramine was significantly better ($p=0.05$) than placebo for sleep latency, degree to which medication helped, depth of sleep, quality, of sleep, feeling rested upon awakening, and degree of energy during previous day. At the less conservative 0.10 level of significance, diphenhydramine was better than placebo for the amount of time spent awake in bed.

Side effects in both studies were low with expected side effects of drowsiness, dizziness, and grogginess occurring more frequently in the diphenhydramine group. The differences in other side effects between the treatment and placebo groups were not significant. The agency concludes that these studies demonstrate that diphenhydramine hydrochloride in a dose of 50 mg is safe and effective as an OTC nighttime sleep-aid.

The agency's detailed comments and evaluation of the data are on file in the Dockets Management Branch (Refs. 13 and 14).

In a notice published in the **Federal Register** on April 23, 1982 (47 FR 17740), the FDA's former Bureau of Drugs concluded that the studies described above (Refs. 1 through 12) resolved safety and effectiveness issues that had been raised when the advance notice of proposed rulemaking and notice of proposed rulemaking were published in the **Federal Register**. The Bureau determined, after reviewing all of the submitted data, that 50 mg diphenhydramine hydrochloride and 76 mg diphenhydramine citrate were appropriate dosage levels in drug products intended for use as OTC nighttime sleep-aids. The Bureau concluded that the citrate salt could be considered identical to the hydrochloride salt because the citrate salt is rapidly converted in the stomach to the hydrochloride salt. However, a dose of 76 mg diphenhydramine citrate is necessary to supply a diphenhydramine content equivalent to 50 mg diphenhydramine hydrochloride.

The notice also announced an enforcement policy to permit the OTC marketing of diphenhydramine as an ingredient in nighttime sleep-aid drug products. The enforcement policy permits the OTC marketing of such drug products pending establishment under the OTC drug review of a final monograph under which drug products containing diphenhydramine that are intended for use as OTC nighttime sleep-aids will be generally recognized as safe and effective and not misbranded.

The notice provided interested persons an opportunity to submit written comments for determining whether further amendments to, or revisions of, this policy are warranted. In response to the notice, the Drug Enforcement Administration, U.S. Department of Justice and one individual submitted comments. The comment from the Drug Enforcement Administration was concerned with the drug abuse potential of diphenhydramine and is addressed in comment 23 below.

The other comment requested clarification as to which of the 12 unpublished studies was the basis for the conclusion that safety and effectiveness issues previously raised were resolved. The comment further stated that such information is needed because information obtained by the commentor under the Freedom of Information Act reveals that at least two of the 12 studies (Refs. 6 and 7) were found to be grossly deficient and unacceptable during establishment inspections by the FDA.

In 1980, FDA investigators did visit the researchers of the unpublished studies (Refs. 6 and 7) to evaluate the clinical trials with diphenhydramine hydrochloride as an OTC nighttime sleep-aid. The agency agrees that some violations in the protocol were found. However, the agency has determined that these violations, for the most part, were minor, and the agency feels that it is unlikely that they could have had a significant impact on the results.

In summary, the agency concludes that the submitted data provide sufficient evidence to demonstrate general recognition of the safety and effectiveness of diphenhydramine hydrochloride in a dose of 50 mg and diphenhydramine citrate in a dose of 76 mg for use as an OTC nighttime sleep-aid, and these ingredients are included in the final monograph.

References

(1) Sunshine, A., and E. Laska, "A Comparative Study of Diphenhydramine 50 mg and Placebo," unpublished study No. S-2162A, Comment Nos. 0B0018, SUP002, and C00035, Docket No. 75N-0244, Dockets Management Branch.

(2) Sunshine, A., and E. Laska, "A Comparative Study of Diphenhydramine 50 mg and Placebo," unpublished study No. S-2162B, Comment Nos. 0B0018, SUP002, and C00035, Docket No. 75N-0244, Dockets Management Branch.

(3) Sunshine, A., I. Zighelboim, and E. Laska, "Hypnotic Activity of Diphenhydramine, Methapyrilene, and Placebo," unpublished study No. W-2080, Comment Nos. 0B0018, SUP002, and C00035, Docket No. 75N-0244, Dockets Management Branch.

(4) Glassman, S., and E.W. Packman, "Subjective Evaluation of the Incidence of Side Effects Produced by 50 mg and 100 mg Doses of Diphenhydramine HCl Versus Placebo," unpublished study No. S-2519, Comment No. SUP002, Docket No. 75N-0244, Dockets Management Branch.

(5) Smith, P. H., "Pain/Sedative Study," unpublished study No. S-2512, Comment Nos. SUP003 and C00035, Docket No. 75N-0244, Dockets Management Branch.

(6) Rickels, K., "Double-Blind, Controlled Evaluation of Diphenhydramine and Placebo in Insomniac General Practice Patients," unpublished study, Comment Nos. C00030, SUP004, and SUP005, Docket No. 75N-0244, Dockets Management Branch.

(7) Finnerty, R., and H. Goldberg, "Double-Blind, Controlled Evaluation of Diphenhydramine and Placebo in Insomniac General Practice Patients," unpublished study, Comment Nos. C00030, SUP004, and SUP005, Docket No. 75N-0244, Dockets Management Branch.

(8) Holder, A., and K.J. Kohlhof, "Assessment of the Sleep Prolongation Properties of Two Analgesic/Sedative Tablets Versus Placebo in Healthy Adults," unpublished study No. S-2593, Comment Nos. C00032 and C00035, Docket No. 75N-0244, Dockets Management Branch.

(9) Sunshine, A., and E. Laska, unpublished study No. S-2127, Comment Nos. 0B0018, SUP002, and C00035, Docket No. 75N-0244, Dockets Management Branch.

(10) Sunshine, A., and I. Zighelboim, "Subjective Clinical Evaluation of the Relative Analgesic/Sedative Effects of an Analgesic/Sedative Tablet vs. Placebo," unpublished study No. S-2469, Comment Nos. C00032 and C00035, Docket No. 75N-0244, Dockets Management Branch.

(11) Sunshine, A., and C. Roure, "Subjective Clinical Evaluation of the Analgesic/Sedative Effects of an Analgesic/Sedative Tablet vs. Placebo," unpublished study No. S-2591, Comment Nos. C00032 and C00035, Docket No. 75N-0244, Dockets Management Branch.

(12) Furst, D., and L. Winter, "Subjective Clinical Evaluation of the Sedative Effects of Two Analgesic/Sedative Tablets vs. Placebo," unpublished study No. S-2605, Comment Nos. C00032 and C00035, Docket No. 75N-0244, Dockets Management Branch.

(13) Letter from W. E. Gilbertson, FDA, to B. M. Lanman, Bristol Myers Products, coded LET004, Docket No. 75N-0244, Dockets Management Branch.

(14) Letter from W. E. Gilbertson,. FDA, to R. A. Schultz, The J. B. Williams Company, Inc., coded LET006, Docket No. 75N-0244, Dockets Management Branch.

23. One comment was concerned with the drug abuse potential of diphenhydramine. The comment submitted data from the Drug Enforcement Administration's (DEA) System to Retrieve Information from Drug Evidence (STRIDE) and argued that the data show significant current problems relating to abuse and trafficking of diphenhydramine that may pose a serious risk to the public health (Ref. 1). The comment added that diphenhydramine was involved in 36

criminal investigations between 1975 and 1982, but because diphenhydramine is not scheduled in the Controlled Substances Act, it is not a primary object of those criminal investigations in which it is encountered.

The comment noted that data from the Drug Abuse Warning Network (DAWN) compiled by the National Institute on Drug Abuse (NIDA) have ranked diphenhydramine in the "Top 50" list of drugs mentioned in overdose cases seen in hospital emergency rooms and that for the period from January to July of 1981, diphenhydramine ranked 27th on the list, higher than many controlled substances, including methadone, LSD, barbiturates, ethchlorvynol, codeine, meprobamate, meperidine, amphetamine, oxazepam, and hydromorphone (Ref. 2). The comment added that, in 1981, 29 percent (396) of the overdose victims included in the DAWN data used diphenhydramine alone, and the remaining 71 percent (961) used diphenhydramine in various combinations. The comment stated that the motivation for taking diphenhydramine was attributed to psychic effects or dependence in 25 percent, or 333 cases, and suicide attempts in 58 percent, or 781 cases. The comment pointed out that the main source of diphenhydramine for an overdose victim was through legal prescription, but that between 1979 and 1981, a significant and increasing source of the drug was from illicit sources—thefts and "street buys."

The comment urged FDA to consider the STRIDE and DAWN data prior to issuing rules that would make diphenhydramine more available to the drug abuse community, i.e., through OTC marketing. The comment argued that, in addition to STRIDE and DAWN data, the diphenhydramine abuse portrait includes diversion from foreign drug manufacturers, transportation to clandestine laboratories in South America, illicit formulation into methaqualone "look-alikes," smuggling into the United States, and domestic pharmacy theft.

The agency has reviewed the data submitted by the comment and concludes that these data do not present a clear picture of deliberate misuse and abuse of diphenhydramine, nor do they show that diphenhydramine marketed OTC as a nighttime sleep-aid at a recommended dose of 50 mg of diphenhydramine hydrochloride or 76 mg of diphenhydramine monocitrate is likely to become a serious risk to public health through abuse.

The STRIDE data illustrate that diphenhydramine had been used to produce counterfeit methaqualone tablet's, but do not show that diphenhydramine was in demand for itself. An illicit international trade in both the commercially manufactured and the clandestinely manufactured counterfeit methaqualone tablets used to exist with a wide geographic distribution. However, FDA has removed methaqualone from the United States market. (See the **Federal Register** of September 17, 1984; 49 FR 36441.) Therefore, the agency does not believe that the counterfeiting program that previously existed is a sufficient basis to keep diphenhydramine off the OTC market.

An overdose per se does not necessarily mean that the drug in question is a drug of abuse. Certainly, so far as the trafficking and diversion data are concerned, it appears that diphenhydramine was primarily a drug of deceit and only secondarily a drug of abuse. With reference to the listing of diphenhydramine in the DAWN "Top 50" list, the agency questions whether the overdose victims were knowingly taking diphenhydramine or whether they were taking diphenhydramine manufactured to resemble a prescription drug product containing methaqualone and represented to them as methaqualone. A number of OTC drugs have been involved in the illicit look-alike drug market, and the agency is convinced of the seriousness of the situation. However, misuse of a drug such as diphenhydramine that occurs because the drug is represented as a more potent substance does not necessarily mean that the drug itself is a drug of abuse. (See also comment 10 above.)

The agency is concerned about the possibility of any adverse effects resulting from the use of OTC drug products, but it also recognizes that a number of substances in the marketplace have the potential for misuse by some individuals. However, this is not sufficient reason for withholding such drugs from legitimate OTC uses for which they are safe and effective. The reports of diphenhydramine abuse cited by the comment do not indicate a widespread problem, nor do they show any correlation between this abuse and OTC marketing of the drug. Therefore, at this time the agency finds no reason why diphenhydramine should not be available OTC as a nighttime sleep-aid. Nevertheless, the agency will continue to monitor this situation carefully and will take appropriate action if additional information should become available concerning diphenhydramine abuse as a result of OTC marketing.

References

(1) Trafficking Information on Diphenhydramine Retrieved from STRIDE, January 1975 to April 1982, OTC Volume 050FM, Docket No. 75N-0244, Dockets Management Branch.

(2) Top Fifty Estimates of Specific Drug Mentions, OTC Volume 050FM, Docket No. 75N-0244, Dockets Management Branch.

F. Comments on Scopolamine

24. One comment requested the agency to reconsider the Category II classification of scopolamine compounds and reclassify these ingredients in Category III for use in combination with other OTC nighttime sleep-aid ingredients.

The agency's conclusions on scopolamine compounds as nighttime sleep-aid ingredients were previously set forth in the tentative final monograph on OTC nighttime sleep-aid drug products (43 FR 25544 at 25548 and 25575–25578). The comment has provided no reason to alter these conclusions, nor have any new data been submitted to the agency since publication of the tentative final monograph. Therefore, scopolamine compounds will not be included in the OTC nighttime sleep-aid final monograph.

II. Summary of Significant Changes to the Proposed Rule

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

2. The claim "reduces time to fall asleep if you have difficulty falling asleep" has been added to the indications section of the monograph. The indication "helps fall asleep" has been revised to read "helps you fall asleep if you have difficulty falling asleep." (See comment 12 above.)

3. The definition of a nighttime sleep-aid has been revised slightly. (See comment 12 above.)

4. The warning in § 338.50(c)(3) 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 2200 at 2215.) The previously proposed requirement that this warning be in type at least twice the size as other warnings is not

being included in the final monograph because the agency believes that all warnings for OTC nighttime sleep-aids are important and should be displayed with equal prominence on the label.

5. The warning in § 338.50(c)(4) has been expanded and revised to read "Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor." (See comment 16 above.)

6. The directions for nighttime sleep-aids in the proposed and tentative final monographs stated "* * * once daily at bedtime * * *." The agency believes that the phrase "once daily" implies that these products are to be taken every day, when in fact they should be taken only if the user has difficulty in falling asleep. Therefore, the directions in the final monograph have been revised to state that the dose is to be taken "* * * at bedtime if needed * * *" instead of "* * * once daily at bedtime * * *."

7. 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 other applicable OTC drug regulations will give manufacturers the option of using either the word "physician" or the word "doctor." This final monograph includes that option. (See § 338.50(e).)

8. The agency's final decision on the appropriateness of a combination of a nighttime sleep-aid and an internal analgesic(s) is not being addressed at this time, but will be addressed in a future issue of the **Federal Register**. (See comment 20 above.)

9. The ingredients doxylamine succinate, phenyltoloxamine dihydrogen citrate, and pyrilamine maleate were listed in the tentative final monograph as Category III ingredients (43 FR 25579). Because no additional data were submitted that establish the general recognition of safety and effectiveness of these ingredients as OTC nighttime sleep aids, they are not included in the final monograph. (See also comment 21 above.) However, OTC nighttime sleep-aid drug products containing doxylamine succinate are presently being marketed under approved NDA's. The agency advises that the marketing status of those products is unaffected by this final monograph.

10. Diphenhydramine hydrochloride and diphenhydramine citrate are included in the monograph for use as OTC nighttime sleep-aids. (See comment 22 above.)

III. The Agency's Final Conclusions on OTC Nighttime Sleep-Aid Drug Products

Based on the available evidence, the agency is issuing a final monograph establishing conditions under which OTC nighttime sleep-aid drug products are generally recognized as safe and effective and not misbranded. Specifically, the agency has determined that the only ingredients that have been determined to be monograph conditions are diphenhydramine hydrochloride and diphenhydramine citrate. All other ingredients considered in this rulemaking have been determined to be nonmonograph conditions for use as a nighttime sleep-aid: doxylamine succinate, methapyrilene fumarate, methapyrilene hydrochloride, phenyltoloxamine dihydrogen citrate, pyrilamine maleate, ammonium bromide, potassium bromide, sodium bromide, scopolamine aminoxide hydrobromide, scopolamine hydrobromide, acetaminophen, aspirin, salicylamide, thiamine hydrochloride, and passion flower extract. Any drug product marketed for use as an OTC nighttime sleep-aid that is not in conformance with the monograph (21 CFR Part 338) may 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 of the act (21 U.S.C. 352) and may not be marketed for this use unless it is the subject of an approved NDA. There are several nighttime sleep-aid drug products containing doxylamine succinate that are presently being marketed OTC under approved NDA's. The agency advises that the marketing status of those products is unaffected by this final monograph. If any drug manufacturer believes that there are adequate data establishing general recognition of the safety and effectiveness of doxylamine succinate as an OTC nighttime sleep-aid, such data may be submitted in an appropriate citizen petition to amend the monograph. (See 21 CFR 10.30.)

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 nighttime sleep-aid 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 nighttime sleep-aid drug products because the proposed rule was issued prior to January 1, 1981, and is therefore exempt.

The agency has determined under 21 CFR 25.24(c)(6) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects in 21 CFR Part 338

Labeling, Nighttime sleep-aid drug products, Over-the-counter drugs.

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 by adding new Part 338, to read as follows:

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

Subpart A—General Provisions

Sec.
338.1 Scope.
338.3 Definition.

Subpart B—Active Ingredients

338.10 Nighttime sleep-aid active ingredients.

Subpart C—Labeling

338.50 Labeling of nighttime sleep-aid drug products.

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

§ 338.1 Scope.

(a) An over-the-counter nighttime sleep-aid drug product in a form suitable

for oral administration is generally recognized as safe and effective and is not misbranded if it meets each condition in this part and each general condition established in § 330.1 of this chapter.

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

§ 338.3 Definition.

As used in this part:

Nighttime sleep-aid. A drug that is useful for the relief of occasional sleeplessness by individuals who have difficulty falling asleep.

Subpart B—Active Ingredients

§ 338.10 Nighttime sleep-aid 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 § 338.50(d):

(a) Diphenhydramine hydrochloride.

(b) Diphenhydramine citrate.

Subpart C—Labeling

§ 338.50 Labeling of nighttime sleep-aid drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "nighttime sleep-aid."

(b) *Indications.* The labeling of the product states, under the heading "Indications," one or more of the phrases listed in this paragraph. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph (b), may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) ("Helps you" or "Reduces time to") "fall asleep if you have difficulty falling asleep."

(2) "For relief of occasional sleeplessness."

(3) "Helps to reduce difficulty falling asleep."

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

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

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

(3) "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."

(4) "Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor."

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

(1) *For products containing diphenhydramine hydrochloride identified in § 338.10(a).* Adults and children 12 years of age and over: Oral dosage is 50 milligrams at bedtime if needed, or as directed by a doctor.

(2) *For products containing diphenhydramine citrate identified in § 338.10(b).* Adults and children 12 years of age and over: Oral dosage is 76 milligrams at bedtime if needed, 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.

Dated: January 17, 1989.

Frank E. Young,

Commissioner of Food and Drugs.

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