DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 75N-0244]

Diphenhydramine; Marketing Status as a Nighttime Sleep-Aid Drug Product for Over-the-Counter Human Use; Notice of Enforcement Policy

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing an enforcement policy to permit the over-the-counter (OTC) marketing of diphenhydramine as an ingredient in nighttime sleep-aid drug products. The enforcement policy will permit the OTC marketing of such drug product 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.

EFFECTIVE DATE: The enforcement policy is effective April 23, 1982.

ADDRESS: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

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

SUPPLEMENTARY INFORMATION: FDA is announcing an enforcement policy concerning the OTC marketing of nighttime sleep-aid drug products containing diphenhydramine. Prior policy could appear to bar OTC marketing of nighttime sleep-aid drug products containing diphenhydramine until such time as FDA has determined that the drug was generally recognized as safe and effective and not misbranded for OTC drug marketing and had published an appropriate OTC monograph in the Federal Register. Under the policy announced below and under the amended enforcement policy statement published elsewhere in this issue of the Federal Register, such products may be marketed immediately.

The OTC drug review procedures are set out in Part 330 (21 CFR Part 330). In accordance with those procedures, FDA published in the Federal Register of December 8, 1975 (40 FR 57292) 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, Sleep-Aid, and Tranquilizer Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in nighttime sleep-aids.

Among the nighttime sleep-aid ingredients reviewed by the Panel was diphenhydramine. This ingredient has been marketed for many years under an approved new drug application for prescription use for several indications. The Panel stated that clinical experience with the ingredient strongly suggested it would be safe and effective as an OTC nighttime sleep-aid. Because of a scarcity of studies for the sleep indication, however, the Panel recommended in its report that the ingredient be classified in Category III (data are insufficient to determine general recognition of safety and effectiveness). The Panel also suggested that OTC marketing be permitted while final testing was carried out. The agency, however, declined to allow marketing at that time. FDA stated that nighttime sleep-aid drug products containing diphenhydramine could not be marketed lawfully for OTC use until tests and studies had been conducted that resolved the questions raised by the Panel, and until the drug was determined by FDA to be generally recognized as safe and effective and not misbranded for OTC marketing and FDA had so indicated in an appropriate monograph published in the Federal Register. The agency's position was in accord with an enforcement policy proposed in the Federal Register of December 4, 1975 (40 FR 56675), published in final form on April 4, 1976 (41 FR 32580), and codified in 21 CFR 330.13.

When the proposed rulemaking (tentative final monograph) for nighttime sleep-aids was published on June 13, 1978 (43 FR 25544), FDA reiterated its ban on OTC marketing of sleep-aids containing diphenhydramine pending completion of the studies and classification of the ingredient in Category I (generally recognized as safe and effective and not misbranded) in the final monograph. The Commissioner of Food and Drugs noted then that evidence at hand strongly suggested that diphenhydramine in an appropriate dosage could prove effective as an OTC nighttime sleep-aid. The Commissioner stated, however, that before there could be a change in the marketing status of nighttime sleep-aid drug products containing diphenhydramine, at least two adequate and well-controlled studies were required.

Subsequently, J. B. Williams Co., Inc., and Bristol-Myers Co. submitted 12 studies (Refs. *1* through *12*) to support the use of diphenhydramine as an OTC nighttime sleep-aid ingredient. Diphenhydramine hydrochloride was evaluated in eight of the studies, and diphenhydramine monocitrate was evaluated in the other four.

After reviewing the submitted studies, FDA's Bureau of Drugs concluded that the studies resolved safety and effectiveness issues that had been raised when the advance notice of proposed rulemaking and proposed rulemaking were published in the Federal Register. The Bureau determined, after reviewing all of the submitted data, that 50 milligrams (mg) diphenhydramine hydrochloride and 76 mg diphenhydramine monocitrate were appropriate dosage levels in drug products intended for use as OTC nighttime sleep-aids. The Bureau concluded that the monocitrate salt could be considered identical to the hydrochloride salt because the monocitrate salt is rapidly converted in the stomach to the hydrochloride salt. However, a dose of 76 mg diphenhydramine monocitrate is necessary to supply a diphenhydramine content equivalent to 50 mg diphenhydramine hydrochloride. The Bureau also concluded that, based on the information available at that time, the studies would provide a sufficient basis to reclassify diphenhydramine from Category III to Category I when a decision was made on the classification of the drug in the final monograph. By letters dated July 18, 1981, the Bureau notified the two firms of its conclusions. These letters have been placed in the Dockets Management Branch (address above) along with the following information. The letters and information may be seen by interested persons from 9 a.m. to 4 p.m. Monday through Friday.

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 C0035, 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 C0035, 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 C0035, 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 C0035, 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. C0030, 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. C0030, 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. C0032 and C0035, Docket No. 75N–0244, Dockets Management Branch.

(9) Sunshine, A., and E. Laska, Unpublished Study No. S–2127, Comment Nos. 0B0018, SUP002, C0035, 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. C0032 and C0035, 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. C0032 and C0035, 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. C0032 and C0035, Docket No. 75N–0244, Dockets Management Branch.

The enforcement policy now set out in § 330.13 (21 CFR 330.13) could appear to bar marketing of nighttime sleep-aid drug products containing diphenhydramine until the final monograph for OTC nighttime sleep-aids is issued. Such drug products would be barred from marketing even though the studies discussed earlier resolved the safety and effectiveness issues that originally resulted in classification of the ingredient in Category III rather than in Category I. The agency has determined that such a result would not be in the public interest. Because currently there are no unresolved safety or effectiveness issues relating to the use of diphenhydramine as a nighttime sleep-aid, it would be inappropriate to continue to bar the interim marketing of such products. Elsewhere in this issue of the **Federal Register**, the agency has amended the statement of enforcement policy in § 330.13 to clarify the agency's enforcement policy with respect to such products. As amended, that statement makes it clear that the Commissioner may, by notice in the **Federal Register**, permit interim marketing of such products.

Accordingly, the Commissioner advises that any drug product intended for use as an OTC nighttime sleep-aid that contains diphenhydramine hydrochloride or diphenhydramine monocitrate in dosages discussed above may be marketed pending issuance of the final monograph, subject to the risk that the Commissioner may, in the final monograph, adopt a different position that could require relabeling, recall, or other regulatory action. Marketing of such a product with labeling not in accord with the tentative final monograph also may result in regulatory action against the product, the marketer, or both.

Interested persons may submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857. Such comments will be considered in determining whether further amendments to or revisions of this policy are warranted. Three copies of all comments shall be submitted, except that individuals may submit single copies of comments. The comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: February 5, 1982.

Mark Novitch,

Acting Commissioner of Food and Drugs.

Dated: March 30, 1982.

Richard S. Schweiker,

Secretary of Health and Human Services.

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