DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 81N-0040]

Insect Repellent Drug Products for Over-the-Counter Oral Human Use;

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking that would establish that over-the-counter (OTC) insect repellent drug products for oral use are not generally recognized as safe and effective and are misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products and the public comment on an advance notice of proposed rulemaking that was based on those recommendations. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by August 9, 1983. New data by June 11, 1984. Comments on the new data by August 10, 1984. These dates are consistent with the time periods specified in the agency's revised procedural regulations for reviewing and classifying OTC drugs (21 CFR 300.10).

ADDRESS: Written comments, objections, new data, or requests for oral hearing 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, National Center for Drugs and Biologics (HFN-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of January 5, 1982 (47 FR 424) FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking that would classify OTC insect repellent drug products for oral use as not generally recognized as safe and effective and as being misbranded and would declare these products to be new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)). The notice was based on the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by April 5, 1982. Reply comments in response to comments filed in the initial comment period could be submitted by May 5, 1982.

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 (address above). In response to the advance notice of proposed rulemaking, one consumer submitted a comment. A copy of the comment is on public display in the Dockets Management Branch.

In this proposed rule to amend Part 310 by adding to Subpart E new § 310.529 (21 CFR 310.529), FDA states for the first time its position on OTC insect repellent drug products for oral use. Final agency action on this matter will occur with the publication at a future date of a final rule relating to OTC insect repellent drug products for oral use.

This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC insect repellent drug products for oral use, based on the comment received and the agency's independent evaluation of the Panel's report. As discussed in the final rule revising the procedural regulations for reviewing and classifying OTC drug, FDA will no longer use 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 rule stage, but will use instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). (See the **Federal Register** of September 29, 1981; 46 FR 47730.) This document retains the concepts of Categories I, II, and III at the proposed rule stage.

In the advance notice of proposed rulemaking, the agency stated that if it proposed to adopt the Panel's recommendation it would propose that insect repellent drug products for oral use be eliminated from the OTC market effective 6 months after the date of publication of a final rule in the **Federal Register**, regardless of whether further testing was undertaken to justify their future use. Based on all information available to date, the agency is proposing that oral insect repellents as a class of drugs be found to be ineffective. If this proposed finding is adopted in the final rule, the agency advises that the conditions under which the drug products that are subject to this rule are not generally recognized as safe and effective and are misbranded (nonmonograph conditions) will be effective 6 months after the date of publication of the final rule in the **Federal Register.** On or after that date, no OTC drug products that are subject to the rule may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved NDA. Manufacturers are encouraged to comply voluntarily with the proposed rule at the earliest possible date.

I. The Agency Tentative Conclusion on the Comment

One comment objected to the Category II clasification of thiamine hydrochloride (vitamin B-1) as an oral insect repellent and claimed that the effectiveness of this ingredient aganist black flies and other biting flies has been demonstrated by sportsmen, conservationists, and other persons engaged in outdoor activities. Maintaining that the Panel's conclusions on thiamine hydrochloride are contradictory, the comment explained that the Panel classified thiamine hydrochloride as Category II, but stated at 47 FR 426 that this ingredient is generally recognized as safe in oral doses up to 40 milligrams (mg) daily and further stated that it did not believe that doses exceeding 40 mg are unsafe. The comment added that the Panel also stated at 47 FR 426 that "of the substances studied, only thiamine hydrochloride (vitamin B-1) has shown enough promise to have been evaluated to any significant degree." The comment claimed that thiamine hydrochloride as an oral insect repellent deserves the same opportunity as other OTC products "to be accepted or rejected by the American consumer" unless the agency proves the ingredient to be unsafe or dangerous.

The agency has reviewed the Panel's recommendations and notes that while the Panel did indicate at 47 FR 426 that thiamine hydrochloride "has shown enough promise to have been evaluated," the submitted studies were inadequate. The Panel concluded, and the agency concurs, that available data do not show that thiamine hydrochloride is an effective oral insect repellent, or that it is generally recognized as such.

Further, the comment did not submit adequate data to support the effectiveness of thiamine hydrochloride as an OTC oral insect repellent. In the absence of adequate data demonstrating that thiamine hydrochloride is generally recognized as effective for use as an oral insect repellent, the ingredient cannot be included as an allowable ingredient in an OTC drug monograph.

II. The Agency's Tentative Adoption of the Panel's Report

FDA has considered the comment and other data and information available at this time and concludes that it will tentatively adopt the Panel's report and recommendation that thiamine hydrochloride labeled for use as an insect repellent for oral use are classified Category II.

The agency is also revising § 310.529(b) to clarify that a product covered by the regulation is a new drug for which an approved NDA is required for marketing, and in the absence of an approved NDA the product would also be misbranded under section 502 of the Act.

The agency has examined the economic consequences of this proposed rulemaking 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 proposed rule for OTC insect repellent drug products for oral use, 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, this particular rulemaking for OTC insect repellent drug products for oral use is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invited public comment in the advance notice of proposed rulemaking regarding any impact that this rulemaking would have on OTC insect repellent drug products for oral use. No comments were received. Any comments on the agency's initial determination of the economic consequences of this proposed rulemaking should be submitted by August 9, 1983. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined that under 21 CFR 25.24(d)(9) (proposed in the **Federal Register** of December 11, 1979; 44 FR 71742) this proposal is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects in 21 CFR Part 310

New drugs.

PART 310—[AMENDED]

Therefore, under the Federal Food, Drug, and Cosmetic Act (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 77 Stat. 948 (21 U.S.C. 321(p), 352 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 as revised (see 47 FR 16010; April 14, 1982), it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended in Part 310 by adding to Subpart E new § 310.529, to read as follows:

§ 310.529 Drug products containing active ingredients offered over-the-counter (OTC) for oral use as insect repellents.

(a) Thiamine hydrochloride (vitamin B–1) has been marketed as an ingredient in over-the-counter (OTC) drug products for internal use as an insect repellent (an orally administered drug product intended to keep insects away). There is a lack of adequate data to establish the effectiveness of this, or any other, ingredient for OTC internal use as an insect repellent. Labeling claims for OTC orally administered insect repellent drug products are either false, misleading, or unsupported by scientific data. The following claims are examples of some that have been made for orally administered OTC insect repellent drug products: "Oral mosquito repellent," "mosquitos avoid you," "bugs stay away," "keep mosquitos away for 12 to 24 hours," and "the newest way to fight mosquitos." Therefore, any drug product containing ingredients offered for internal use as an insect repellent cannot be generally recongnized as safe and effective.

(b) Any OTC drug product that is labeled, represented, or promoted for internal use as an insect repellent is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act, for which an approved new drug application under section 505 of the act and Part 314 of this chapter is required for marketing. In the absence of an approved new drug application, such product is also misbranded under section 502 of the act.

(c) A completed and signed "Notice of Claimed Investigational Exemption for a New Drug" (Form FD–1571) (OMB Approval No. 0910–0014), as set forth in § 312.1 of this chapter, is required to cover clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted OTC as an insect repellent for internal use is safe and effective for the purpose intended.

(d) After the effective date of the final regulation, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

Interested persons may, on or before August 9, 1983, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner. A request for an oral hearing must specify points to be covered and time requested. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief.

Comments, objection, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register**.

Interested persons, on or before June 11, 1984, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three

copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA-305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final rule, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on August 10, 1984. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final rule is published in the Federal Register, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Mark Novitch,

Acting Commissioner of Food and Durgs.

Margaret M. Heckler,

Secretary of Health and Human Services.

Dated: May 19, 1983.

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