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, HHS.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing an advance notice of proposed rulemaking that would classify insect repellent drug products for over-the-counter (OTC) oral human use as not generally recognized as safe and effective and as being misbranded. This notice is based on the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments by April 5, 1982, and reply comments by May 5, 1982.

ADDRESS: Written comments to the Dockets Management Branch (formerly the Hearing Clerk's Office) (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: In accordance with Part 330 (21 CFR Part 330), FDA received on June 7, 1980 a report on insect repellent drug products for oral use from the Advisory Review Panel on OTC Miscellaneous Internal Drug Products. FDA regulations (21 CFR 330.10(a)(6)) provide that the agency issue in the Federal Register a proposed order containing: (1) The monograph recommended by the Panel, which establishes conditions under which OTC insect repellent drug products for oral use are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs' not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify such conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

The Panel's recommendations on OTC insect repellent drug products for oral use contain no Category I or Category III conditions, and FDA is issuing the Panel's recommendations proposing Category II classification of OTC insect repellent drug products for oral use.

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The report has been prepared independently of FDA, and the agency has not yet fully evaluated the report. This document represents the best scientific judgment of the Panel members, but does not necessarily reflect the agency's position on any particular matter contained in it. The Panel's findings appear in this document to obtain public comment before the agency reaches any decision on the Panel's recommendations that the ingredients in insect repellent drug products for oral use be classified as Category II. If the agency proposes to adopt the Panel's recommendations, a regulation declaring these products to be new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)) will be proposed for inclusion in Part 310, Subpart E (21 CFR Part 310, Subpart E). The agency is including, in this advance notice of proposed rulemaking, a regulation based upon the Panel's recommendations in order to obtain full public comment at this time.

After reviewing all comments submitted in response to this document, FDA will publish in the Federal Register a notice of proposed rulemaking on OTC insect repellent drug products for oral use. The agency's position on OTC oral insect repellent drug products will be stated initially when that notice of proposed rulemaking is published in the Federal Register. In the notice of proposed rulemaking, the agency also will announce its intitial determination whether the proposed rule is a major rule under Executive Order 12291 and will consider the requirements of the Regulatory Flexibility Act (5 U.S.C. 601-612). The present notice is referred to as an advance notice of proposed rulemaking to reflect its actual status and to clarify that the requirements of the Executive Order and the Regulatory Flexibility Act will be considered when the notice of proposed rulemaking is published. At that time FDA also will consider whether the proposed rule has a significant impact on the human environment under 21 CFR Part 25 (proposed in the Federal Register of December 11, 1979, 44 FR 71742).

The agency invites public comment regarding any impact that this rulemaking would have on OTC oral insect repellent drug products. Types of impact may include, but are not limited to, the following: Increased costs due to relabeling, repackaging, or reformulating; removal of unsafe or ineffective products from the OTC market; and testing, if any. Comments regarding the impact of this rulemaking on OTC oral insect repellent drug products should be accompanied by appropriate documentation.

If FDA proposes to adopt the Panel's recommendations, the agency will 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 is undertaken to justify their future use.

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was announced in the Federal Register of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the Federal Register of May 11, 1972 (37 FR 9464). In accordance with these regulations, a request for data and information on all active ingredients used in OTC miscellaneous internal drug products was issued in the Federal Register of November 16, 1973 (38 FR 31696). (In making their categorizations with respect to "active" and "inactive" ingredients, the advisory review panels relied on their expertise and understanding of these terms. FDA has defined "active ingredient" in its current good manufacturing practice regulations (§ 210.3(b)(7), (21 CFR 210.3(b)(7))), as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." An "inactive ingredient" is defined in § 210.3(b)(8) as "any component other than an 'active ingredient.'") In the Federal Register of August 27, 1975 (40 FR 38179) a notice supplemented the initial notice with a detailed, but not necessarily all-inclusive, list of active ingredients in miscellaneous internal

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drug products to be considered in the OTC drug review. The list, which did not include oral insect repellent ingredients, was provided to give guidance on the kinds of active ingredients for which data should be submitted. The notices of November 16, 1973, and August 27, 1975, informed OTC drug product manufacturers of their opportunity to submit data to the review at that time and of the applicability of the monographs from the OTC review to all OTC drug products.

Under § 330.10(a) (1) and (5), the Commissioner of Food and Drugs appointed the following Panel to review the data and information submitted and to prepare a report on the safety, effectiveness, and labeling of the active ingredients in these OTC miscellaneous internal drug products:

James L. Tullis, M.D., Chairman (appointed December 1979)
John W. Norcross, M.D., Chairman (resigned March 1979)
Diana F. Rodriguez-Calvert, Pharm. D. (appointed July 1976)
Ruth Eleanor Brown, R.Ph. (resigned May 1976)
Elizabeth C. Giblin, M.N., Ed. D.
Richard D. Harshfield, M.D.
Theodore L. Hyde, M.D.
Claus A. Rohweder, D.O. (deceased April 13, 1979)
Samuel O. Thier, M.D. (resigned November 1975)
William R. Arrowsmith, M.D. (appointed March 1976)

Representatives of consumer and industry interests served as nonvoting members of the Panel. Eileen Hoates, nominated by the Consumer Federation of America, served as the consumer liaison until September 1975, followed by Michael Schulman, J.D., Francis J. Hailey, M.D., served as the industry liaison, and in his absence John Parker, Pharm. D., served. Dr. Hailey served until June 1975, followed by James M. Holbert, Sr., Ph. D. All industry liaison members are nominated by the Proprietary Association.

The following FDA employees assisted the Panel: Armond M. Welch, R.Ph., served as the Panel Administrator until July 1979, followed by John R. Short, R.Ph., Enrique Fefer, Ph. D., served as the Executive Secretary until July 1976, followed by George W. James, Ph. D., until October 1976, followed by Natalia Morgenstern until May 1977, followed by Arthur Auer until October 1978. Roger Gregorio served as the liaison for the Office of New Drug Evaluation beginning November 1978. Joseph Hussion, R.Ph., served as the Drug Information Analyst until July 1976, followed by Anne Eggers, R.Ph., M.S., until October 1977, followed by John R. Short, R.Ph., until July 1979.

In order to expand its scientific base, the Panel called upon Ralph B. D'Agostino, Ph. D., for advice in statistics.

The Advisory Review Panel on OTC Miscellaneous Internal Drug Products was charged with the review of many categories of drugs, but due to the large number of ingredients and varied labeling claims, the Panel decided to review and publish its findings separately for several drug categories and individual drug products. The Panel presents its conclusions and recommendations for oral insect repellent drug products in this document. The review of all other categories of miscellaneous internal drug products is being continued by the Panel, and its findings are being published periodically in the Federal Register.

The Panel was first convened on January 13, 1975, in an organizational meeting. Working meetings which dealt with OTC insect repellent drug products for oral use were held on the following dates: February 23 and 24, April 18 and 19, and June 6 and 7, 1980.

The minutes of the Panel meetings are on public display in the Dockets Management Branch (FHA-305), Food and Drug Administration (address above).

No person requested an opportunity to appear before the Panel to express his or her views on oral insect repellent drug products.

No submissions were made for oral insect repellent drug products; however, the Panel has thoroughly reviewed all available literature and has considered all pertinent data and information through June 7, 1980 in arriving at its conclusions and recommendations for these OTC drug products.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel considered OTC oral insect repellent drug products with respect to the following three categories:

Category I. Conditions under which OTC oral insect repellent drug products are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC oral insect repellent drug products are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

The Panel reviewed one oral insect repellent drug product active ingredient and classified this ingredient in Category II.

A. Submission of Data and Information.

Although oral insect repellents were not listed in the notices published in the Federal Register of November 16, 1973 (38 FR 31696) and August 27, 1975 (40 FR 38179), these requests for submission of data and information were for all OTC miscellaneous internal drug products. No submissions for oral insect repellents were made pursuant to these notices, but the Panel was made aware (by FDA's Bureau of Drugs' Office of Compliance) of oral insect repellent drug products being marketed as follows:

Firms and Marketed Products

Thompson Enterprises, Middleport, NY 14105—E-Z Mosquito Repellent, tablets.
Cordova Laboratories, Sylmar, CA 91342—E-Z Oral Mosquito Bite Relief, tablets.

It appears from the labeling available to the Panel that thiamine hydrochloride is the active ingredient in these products; therefore, this is the only ingredient discussed in this document.

B. General Discussion.

Since antiquity, mosquitos, fleas, and other biting insects have been a source of great annoyance. Within the past century it has been shown that insects are also carriers of many diseases which affect humans and animals. Transmission of malaria and yellow fever by mosquitos are the best known instances of insect-borne disease, and control of the above diseases by mosquito abatement is common knowledge. Nevertheless, these and other insect-transmitted diseases continue to be a problem throughout much of the populated area of the world. In addition to transmission of disease, biting insects are a problem to many people in many areas of the world because of localized reaction and general annoyance. These problems have plagued troops in the field, and the military has been particularly interested in methods of protecting personnel against biting insects.

Numerous efforts have been made to identify the properties or substances which attract mosquitos to humans. Among those studied have been body heat and moisture and the various components of sweat. In a review of this problem, Maibach et al. (Ref. *1*) noted that odor appeared to be more important in attracting the mosquitos from a distance but that heat and moisture were probably more important in determining the site of the bite once the mosquito was in close proximity to the individual. These investigators studied the composition of sweat and separated various components. It appeared that lipid components of sweat had some

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repellent effect on mosquitos and that sweat was more attractive to them when the lipids had been removed from it. Despite this and other studies, the precise explanation of what attracts mosquitos to humans and what might repeal them is still not clear.

Several substances for application to the skin to repeal insects are available and are claimed to be effective. This Panel did not review topical insect repellents, but is cognizant of the fact that these substances tend to be washed away rapidly by perspiration or other moisture. For several decades, studies have been performed directed at identifying substances which could be taken internally and would have prolonged effectiveness in repealing biting insects. In the United States, these studies have been limited almost entirely to mosquito repellents.

Ideally, an oral insect repellent should be nontoxic and should be inactivated or eliminated slowly from the body so that ingestion once or twice daily would be effective against specific insects (e.g., mosquitos, fleas, and tsetse flies), or, better yet, against a wide variety of biting insects. Of the substances studied, only thiamine hydrochloride (vitamin B–1) has shown enough promise to have been evaluated to any significant degree. During its review, the Panel found different terminology, i.e., thiamine hydrochloride, thiamine chloride, and thiamin chloride, used to describe this vitamin B–1 preparation. The Panel concludes that each of these terms refers to thiamine hydrochloride, which is the correct name of this ingredient (Ref. *2*).

In 1943, Shannon (Ref. *3*) reported that thiamin chloride, administered by mouth or by injection, appeared to have a repellent effect on the mosquitos. This has led to further investigation of thiamine hydrochloride as an oral insect repellent, as well as its promotion for that purpose. This Panel has limited its review to drug products which are claimed to repeal mosquitos. However, some of these products had labeling and promotional material which also incorporated claims regarding the drug's ability to allevite symptoms due to the bite. Although the Panel knows of no conclusive data to substantiate "bite relief" claims, a review of these claims is beyond the scope of this document.

References

(*1*) Miabach, H. I., et al., "Human Skin in Relationship to Mosquito Attraction and Repulsion," *Connecticut Medicine*, 33:23–28, 1969.

(*2*) "The United States Pharmacopeia XIX," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 502, 1975.

(*3*) Shannon, W. R., "Thiamin Chloride—An Aid in the Solution of the Mosquito Problem," *Minnesota Medicine*, 26:799–802, 1943.

C. Category II Active Ingredient.

The Panel has classified the following oral insect repellent active ingredient as not generally recognized as safe and effective or as being misbranded for OTC use:

Thiamine hydrochloride. The Panel concludes that thiamine hydrochloride, also known as vitamin B–1, is safe in the dose noted below, but is not an effective oral insect repellent, nor is it generally recognized as such.

1. *Safety.* Thiamine hydrochloride occurs naturally in many foods of plant and animal origin. Because thiamine hydrochloride is not made or stored in the body to any significant degree, daily ingestion is required to maintain good health. This daily requirement is approximately 1 milligram (mg) in the average adult, but varies somewhat depending on age, weight, and type of diet consumed. It is easily met by persons consuming a well-balanced diet.

Absorption of thiamine hydrochloride from the gastrointestinal tract is limited to a maximum of about 15 mg per day, which can be satisfied by the oral administration of 40 mg in divided doeses with food. Any excess beyond bodily requirements is rapidly excreted in the urine either as pyrimidine or thiamine (Ref. *1*).

The Panel, therefore, concludes that thiamine hydrochloride is generally recongized as safe when taken orally in doses up to 40 mg daily. The Panel does not think that dose in excess of 40 mg are unsafe, but it is inappropriate to administer more than is necessary to provide for maximum absorption.

2. *Effectiveness.* In 1943, Shannon (Ref. *2*) reported that thiamin chloride decreased the number of mosquito bites in nine patients including adults, children, and infants. All showed severe reaction to mosquito bites. In another study in 1945 Eder (Ref. *3*) reported thiamin chloride to be effective for preventing flea bites in adults, children, and infants. The species of mosquitos or fleas involved were unidentified, and no control was used in either of the above studies. A later study by Ruiz-Maldonado and Tamayo (Ref. *4*), also uncontrolled, using 200 to 300 mg thiamine chloride daily for up to 6 months in children being treated for papular urticaria (palpable hives presumably caused by insect bites) "* * * suggests that thiamine chloride is a preventive agent for insect prurigo" (papular urticaria). The significance of these results is difficult to determine because one-third of the subjects did not return for evaluation.

Strauss, Maibach, and Khan (Ref. *5*) screened 114 drugs given systemically using an objective measure (probing activity of the *Aedes aegypti* mosquito) and found no significant effect for any of the drugs, including vitamin B–1, in reducing probing activity. Probing activity referes to a test devised by Khan et al. (Ref. *6*) in which a nylon net cage containing six mosquitos is held 1 centimeter above the skin, and the time it takes for three mosquitos to start probing toward the skin is measured. Vitamin B–1 and vitamin B–6 were also tested by Strauss, Maibach, and Khan (Ref. *5*) for their effectiveness in reducing the biting activity of these mosquitos, but no signficant effect was demonstrated.

In a double-blind, placebo-controlled study performed by Khan et al. (Ref. *7*), 200 mg thiamine chloride was given three times daily for 2 days to volunteers. On the third day, after receiving a 200-mg dose of thiamine chloride the subjects were enclosed in a room containing mosquitos (*Aedes aegypti*). No significant difference was found between the number of bites received by the placebo group and the number received by the thiamine chloride-treated group.

In another controlled study, Wilson et al. (Ref. *8*) administered 120 mg of thiamin chloride per day for three days (30 mg four times daily) to three individuals. Repellency tests, using *Aedes aegypti* mosquitos, were started on the second day of treatment. Neither the rate of biting nor the subjects' reactions to the bites differed materially from the three individuals who served as controls.

An unpublished report (Ref. *9*) has indicated no protective effect of thiamine hydrochloride in doses up to 1 gram (g) per day against *Aedes aegypti* mosquitoes.

The Panel, therefore, concludes that thiamine hydrochloride is not an effective oral insect repellent, nor is it generally recognized as such.

3. *Evaluation.* The Panel concludes that thiamine hydrochloride is safe for OTC use, but the available evidence does not indicate that it is effective as an oral insect repellent, nor is it generally recognized as such. The Panel concludes that there are no ingredients that are safe and effective when used as an oral insect repellent.

References

(*1*) Greengard, P., "Water-Soluble Vitamins," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S.

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Goodman and A. Gilman, The MacMillan Co., New York, pp. 1549–1551, 1975.

(2) Shannon, W. R., "Thiamin Chloride—An Aid in the Solution of the Mosquito Problem," *Minnesota Medicine*, 26:799–802, 1943.

(3) Eder, H. L., "Flea Bites—Prevention and Treatment with Thiamin Chloride," *Archives of Pediatrics*, 62:300–301, 1945.

(4) Ruiz-Maldonado, R., and L. Tamayo, "Treatment of 100 Children with Papular Urticaria with Thiamine Chloride," *International Journal of Dermatology*, 12:258–260, 1973.

(5) Strauss, W. G., H. I. Maibach, and A. A. Khan, "Drugs ad Disease as Mosquito Repellents in Man," *The American Journal of Tropical Medicine and Hygiene*, 17:461–464, 1968.

(6) Khan, A. A., et al., "Screening Humans for Degrees of Attractiveness to Mosquitos," *Journal of Economic Entomology*, 58:694–697, 1965.

(7) Khan, A. A., et al., "Vitamin B_1 is not a Systemic Mosquito Repellent in Man," *Transactions of the St. John's Hospital Dermatological Society*, 55:99–102, 1969.

(8) Wilson, C. S., D. R. Mathieson, and L. A. Jachowski, "Ingested Thiamin Chloride as a Mosquito Repellent," *Science*, 100:147, 1944.

(9) OTC Volume 170174 (report of tests performed at the USDA Orlando Laboratory contained in a letter dated July 31, 1959 from Colonel Ralph W. Bunn to Captain John W. Goodner).

D. Category II Labeling.

The Panel concludes that since there are no Category I or Category III ingredients, any labeling which claims insect repellency for an orally administered drug product is considered to be Category II and may not be used.

PART 310—NEW DRUGS

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 72 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 (see 46 FR 26052; May 11, 1981), the agency advises in this advance notice of proposed rulemaking that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations would 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 recognized as safe and effective.

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

(c) A completed and signed "Notice of Claimed Investigational Exemption for a New Drug" (Form FD–1571) 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 April 5, 1982, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before May 5, 1982. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: September 23, 1981.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Dated: December 17, 1981.

Richard S. Schweiker,

Secretary of Health and Human Services.

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