DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Parts 310, 700]

CERTAIN HALOGENATED SALICYLANILIDES AS ACTIVE OR INACTIVE INGREDIENTS IN DRUG AND COSMETIC PRODUCTS

Notice of Proposed Rulemaking

Elsewhere in this issue of the FEDERAL REGISTER the Commissioner of Food and Drugs is issuing a notice of proposed rulemaking setting forth the results of the OTC Antimicrobial I Drug Review Panel's evaluation of over-the-counter (OTC) drug products containing antimicrobial ingredients for topical human use and a proposed monograph establishing conditions under which such products are generally recognized as safe and effective and not misbranded. The discussion in that notice of proposed rulemaking and material supporting it are incorporated by reference in this notice of proposed rulemaking.

Submissions of data and information reviewed by the Panel included those regarding the use of tribromsalan. Tribromsalan (TBS, 3,4'5-tribromosalicylanilide) is a brominated salicylanilide which is used as an active ingredient for antimicrobial purposes and as an inactive ingredient for preservative purposes in OTC drug and cosmetic products. In its report the Panel states that tribromsalan, even when free of related chemicals, can cause photosenstitive eruptions in man and disabling skin disorders. In some instances the photosensitization may persist for prolonged periods as severe reactions without further exposure to the chemical. The Panel also reported that there is evidence to indicate that tribromsalan produces cross-sensitization with other halogenated salicylanilides. In addition to the problem of photosensitization, the Panel expresses concern about the potential toxicity of this compound if used in an antimicrobial soap, intended for daily, total body use, possibly for a lifetime. Animal and human toxicological data made available to the Panel failed to provide a basis for establishment of a safe level for use. The Panel noted that, with regard to effectiveness, there was no clear evidence that tribromsalan does anything other than control body odor, for which other safer agents are available. The Panel recommended to the Commissioner that tribromsalan be considered not safe for general use as an OTC antimicrobial agent in drug and cosmetic products and that the Food and Drug Administration take prompt action to remove tribromsalan from all such products.

Although the Panel did not receive any submissions of data for review regarding the use of halogenated salicylanilides other than tribromsalan, the Panel's report and supporting scientific literature clearly indicate that other halogenated salicylanilides such as dibromsalan (DBS) and tetrachlorosalicylanilide (TCSA) have been shown to be more potent photosensitizers and cross-photosensitizers than tribromsalan. Thus, the Commissioner has determined that any action regarding the use of tribromsalan shall also include these other halogenated salicylanilides.

On the basis of the Panel's report, the Commissioner concludes that these halogenated salicylanilides, including tribromsalan, dibromsalans, and tetrachlorosalicylanilide, cannot be considered as safe for any use in drug and cosmetic products. Therefore, the Commissioner proposes to determine that any drug product containing these halogenated salicylanilides as an active or inactive ingredient is 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 pursuant to section 505 of the act and 21 CFR Part 314 is required. The Commissioner also proposes to determine that these halogenated salicylanilides are deleterious substances which may render any cosmetic product that contains such a halogenated salicylanilide as an ingredient at any level, for any purpose, injurious to users. Accordingly, any such cosmetic product would be deemed to be adulterated under section 601(a) of the act.

The Food and Drug Administration has reviewed its files and has determined that there are no currently approved new drug applications for any prescription or OTC drug products containing a halogenated salicylanilide as an active or inactive ingredient. All previously approved new drug applications for drug products containing a halogenated salicylanilide as an ingredient have either been withdrawn or subsequently amended to delete the halogenated salicylanilides from the product formulation. Where such amendments have been submitted and have been approved or permitted by the Food and Drug Administration, the previous approval of the product formulation containing the halogenated salicylanilide has been revoked and only the product formulation contained in the supplemental new drug application is approved or permitted for marketing under section 505 of the act.

In its report, the Panel indicates that the benefit from using drug and cosmetic products containing these halogenated salicylanilides is insignificant when compared to the risk and, where there is so little benefit, that it is unjustified to subject even a few individuals to such a risk. The Panel recommends that action to remove these chemicals from such products should be implemented expeditiously and should not await the full procedural review that has been established for OTC drug products in 21 CFR 330.10. Accordingly, on the basis of the Panel's concerns, the documented evidence of photosensitization and cross-photosensitization caused by these halogenated salicylanilides, the lack of toxicological data adequate to the establishment if a safe level for use, the availability of other safer agents, the adverse benefit-to-risk ratio, and the recommendation for prompt action to remove these chemicals from all drug and cosmetic products, the Commissioner has determined that the action he proposes regarding the use of these halogenated salicylanilides in such products shall be taken through this notice of proposed rule making. The Commissioner had concluded that any delay in action regarding the use of these halogenated salicylanilides in drug and cosmetic product is unjustified in view of the Panel's report and the evidence now at hand that such use is not safe and is contrary to the public interest.

After publication, the final order regarding the use of these halogenated salicylanilides will apply to all drug and cosmetic products until such time as new evidence on the safety or effectiveness of these chemicals result in amendment of the proposed monograph for OTC antimicrobial products to allow for the use of these chemicals as active or inactive ingredients of such products.

The Commissioner, at this time, does not anticipate that a recall of previously marketed drug and cosmetic products containing these halogenated salicylanilides as an ingredient is necessary to protect the public health. Available information indicates that the largest use of these chemicals in drug and cosmetic products was in antibacterial soaps and that soap formulations have already been changed to delete these chemicals as ingredients.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 505, 601(a), 701(a); 52 Stat. 1052–1055, as amended; 21 U.S.C. 355, 361(a), 371(a)) and under authority delegated to the Commisioner (21 CFR 2.120), it is proposed that Parts 310 and 700 be amended as follows:

1. By adding a new § 310.508 to Subpart E to read as follows:

§ 310.508 Use of certain halogenated salicylanilides as an inactive ingredient in drug products.

(a) Halogenated salicylanilides (tribromsalan (TBS, 3,4',5-tribromsalicylanilide), dibromsalans (DBS, 4',5-dibromosalicylanilide, and 3,5-dibromosalicylanilide), and 3,3',4,5'-tetrachlorosalicylanide (TCSA)) have been used as active or inactive ingredients in a number of over-the-counter (OTC) drug products, largely antibacterial soaps, for antimicrobial, preservative, and other purposes. These halogenated salicylanilides are potent photosensitizers and can cause disabling skin disorders. In some instances the photosensitization may persist for prolonged periods as a severe reaction without further exposure to these chemicals. Safer alternative antimicrobial agents are available.

(b) These halogenated salicylanilides are not generally recognized as safe and effective for use as active or inactive ingredients in any drug products. Therefore, any drug products containing such a halogenated salicylanilide as an ingredient at any level for any purpose is 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 pursuant

to 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 such preparations are safe and effective for the purpose intended.

(d) Any such drug product introduced into interstate commerce that is not in compliance with this section within 30 days after the date of publication of the final order is subject to regulatory action.

2. By adding a new § 700.15 to Subpart B to read as follows:

§ 700.15 Use of certain halogenated salicylanilides as ingredients in cosmetic products.

(a) Halogenated salicylanilides (tribromsalan (TBS, 3,4',5-tribromosalicylanilide), dibromsalans (DBS, 4',5-dibromosalicylanilide, and 3,5-dibromosalicylanilide, and 3,3',4,5'-tetrachlorosayicylanilide (TCSA)) have been used as antimicrobial agents for a variety of purposes in cosmetic products. These halogenated salicylanilides are potent photosensitizers and cross-sensitizers and can cause disabling skin disorders. In some instances the photosensitization may persist for prolonged periods as a severe reaction without further exposure to these chemicals. Safer alternative antimicrobial agents are available.

(b) These halogenated salicylanilides are deleterious substances which render any cosmetic that contains them injurious to users. Therefore, any cosmetic product that contains such a halogenated salicylanilide as an ingredient at any level for any purpose is deemed to be adulterated under section 601(a) of the Federal Food, Drug, and Cosmetic Act.

(c) Any cosmetic product containing these halogenated salicylanilides as an ingredient that is introduced into interstate commerce 30 days after the date of publication of the final order is subject to regulatory action.

Because of the evidence set forth in the preamble which indicates that these halogenated salicylanilides are not safe for use as active or inactive ingredients in drug and cosmetic products, the Commissioner has determined that it is in the public interest to limit the time for public comment to 30 days.

Interested persons are invited to submit their comments (preferably in quintuplicate) regarding this proposal, on or before October 15, 1974, to the Hearing Clerk, Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, MD 20852. Comments may be accompanied by a memorandum or brief in support thereof. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: August 30, 1974.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

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[21 CFR Part 333]

OVER-THE-COUNTER DRUGS

Proposal To Establish a Monograph for OTC Topical Antimicrobial Products

Pursuant to Part 330 (21 CFR Part 330), the Commissioner of Food and Drugs received on July 24, 1974, the report of the Advisory Review Panel on over-the-counter (OTC) antimicrobial drug products for repeated daily human use. In accordance with § 330.10(a)(6), the Commissioner is publishing (1) a proposed regulation containing the monograph recommended by the Panel establishing conditions under which OTC topical antimicrobial drugs are generally recognized as safe and effective and not misbranded, (2) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel 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 on the basis of a determination by the Panel 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 to the Commissioner. The summary minutes of the Panel meetings are on public display in the Office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD. 20852.

The Commissioner cautions that the conclusions and recommendations of the Panel must be read and evaluated carefully, to differentiate hypotheses from proven facts. In particular, substantial controversy has already emerged in the course of the Panel deliberations with respect to the hypothesis that the use of antimicrobial agents in bar soaps may selectively kill non-pathogenic gram positive microorganisms resulting in an increase in pathogenic gram negative microorganisms. The Panel has stated, and the Commissioner recognizes, that this hypothesis has not yet been proved by reliable evidence.

The purpose of issuing the unaltered conclusions and recommendations of the Panel, including this hypothesis, is to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The Commissioner has not yet evaluated the report, but has concluded that it should first be issued as a formal proposal in order to obtain full public comment before any decision is made on the recommendations of the Panel. The report of this Panel represents their best scientific judgment. It has been prepared independent of the Food and Drug Administration and does not necessarily reflect the Agency's position on any particular matter contained therein. After a careful review of this document and all comments submitted in response to it, the Commissioner will prepare a tentative final regulation to establish a monograph for OTC topical antimicrobial products.

The Commissioner has concluded that, to assure implementation of the Panel's recommendations, both cosmetic as well as drug regulations should be promulgated. The present Federal Food, Drug, and Cosmetic Act provides no legal authority under which the Agency can reclassify cosmetics as drugs, but does permit regulation of cosmetic ingredients. It is the Commissioner's intent to propose regulations under sections 601(a) and 602(a) of the act to apply the same safety and labeling standards to cosmetics containing antimicrobial ingredients subject to this notice as are applied to OTC drug products containing these ingredients.

It is also the Commissioner's intent to promulgate regulations in the Tentative Final Monograph to distinguish between preservative and active levels of antimicrobials. While the Commissioner takes no position at this time on the preservative test recommended in the Panel report, it is his intent to require either a preservative test or specific maximum preservative levels for antimicrobial ingredients in OTC drug products and cosmetics.

In accordance with § 330.10(a)(2), all data and information concerning OTC antimicrobial drug products for repeated daily human use submitted for consideration by the Advisory Review Panel have been handled as confidential by the Panel and the Food and Drug Administration. All such data and information shall be put on public display at the office of the Hearing Clerk, Food and Drug Administration on or before October 15, 1974, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality shall be submitted to the Food and Drug Administration, Bureau of Drugs, OTC Drug Products Evaluation Staff (HFD-109), 5600 Fishers Lane, Rockville, MD 20852.

Based upon the conclusions and recommendations of the Panel, the Commissioner proposes, upon publication of the final regulation:

1. That the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

2. That the conditions excluded from the monograph on the basis of the Panel determination that they would result in the drug not being generally recognized as safe and effective or would result in misbranding (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER, regardless whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient to classify such conditions either as generally recognized as safe and effective and not misbranded or as not being generally recognized as safe and effective or would result in misbranding (Category III) be permitted to remain in use for 1 year after the date of publication of the final monograph