INSTRUCTIONS

1. Prepare an original and three copies of this application (CAB Form 85). If extra space is needed to complete an item, continue on a separate sheet of paper.

2. Attach in duplicate the air charter contract and proposed solicitation material. If applicable, enclose filing fees and attach in duplicate contract between charter organizer and passengers; surety bond (include an original copy); and depository agreement.

3. Send the application to: "Civil Aeronautics Board, Attention: Director, Bureau of Operating Rights, Washington, D.C. 20428" in time to be received at least 30 days in advance of commencement of the proposed operation. Applications received less than 30 days prior to the flight departure will be rejected, unless good cause for lateness is shown.

[FR Doc.75-28707 Filed 10-29-75;8:45 am]

Title 21—Food and Drugs

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

[Docket No. 75N-0177]

PART 310—NEW DRUGS

PART 700—COSMETICS

Certain Halogenated Salicylanilides as Active or Inactive Ingredients in Drug and Cosmetic Products

The Commissioner of Food and Drugs has determined that any drug or cosmetic product containing the halogenated salicylanilides, tribromsalan (TBS, 3,4',5 - tribromosalicylanilide), dibromsalan (DBS, 4',5-dibromosalicylanilide), metabromsalan (MBS, 3,5-dibromosalicylanilile) and 3,3',4,5'-tetracholorsalicylanilide (TCSA) is a new drug or an adulterated cosmetic. This regulation regarding these halogenated salicylanilides shall be effective on December 1, 1975.

A notice of proposed rulemaking was published in the FEDERAL REGISTER of September 13, 1974 (39 FR 33102), in which the Commissioner proposed that any drug or cosmetic product containing certain halogenated salicylanilides as active or inactive ingredients is a new drug or an adulterated cosmetic. Elsewhere in that same issue of the FEDERAL REGISTER (39 FR 33103), the Commissioner issued 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 Panel reviewed submissions of data and information regarding the use of tribromsalan. Tribromsalan (TBS, 3, 4',5-tribromosalicylanilide) is a halogenated salicylanilide, which is used in OTC drug and cosmetic products as an active ingredient for its antimicrobial action or as an inactive ingredient as a preservative.

The Panel concluded, in its report, that tribromsalan can photosensitize and cause skin eruptions in man and lead to a disabling skin disorder. In some instances the photosensitization may persist for prolonged periods and severe reactions can reoccur in the presence of sunlight even though the individual is not exposed again to tribromsalan. The Panel also reported that there is evidence to indicate that tribromsalan produces cross-sensitization with other halogenated salicylanilides. In addition to citing the problem of photosensitization, the Panel expressed concern about the potential toxicity of this compound if used over an extended period of time. Such exposure would occur if tribromsalan were used in an antimicrobial soap, which is intended for daily use over the entire body and may be used for a lifetime. Although extensive animal and human toxicological data were reviewed by the Panel concerning the amount absorbed through the skin and length of use, the data failed to provide a basis for establishment of a safe level for use. The Panel noted that, although tribromsalan contributes to control of body odor, there are other safer agents available that achieve the same result.

The Panel recommended to the Commissioner that tribromsalan and certain chemically related halogenated salicylanilides also reviewed by the Panel be considered not safe for general use as OTC antimicrobial agents in drug and costmetic products, and that the Food and and Drug Administration take prompt action to remove such ingredients from all products.

The report of the Panel and supporting scientific literature clearly indicate that certain halogenated salicylanilides such as dibromsalan (DBS), metabromsalan (MBS) 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 use of tribromsalan shall also include these other halogenated salicylanilides.

Interested persons were invited to submit written comments regarding the proposal on these halogenated salicylanilides on or before October 15, 1974. Requests for extensions of time to comment on the proposal were received, and the Commissioner permitted additional time through January 13, 1975, on the assurance from the major manufacturer that sales in the United States of halogenated salicylanilides were virtually nil.

The Commissioner has carefully reviewed all of the comments and also again reviewed the findings of the OTC Antimicrobial I Drug Review Panel regarding halogenated salicylanilides (tritribomsolar (TBS, 3,4',5-tribromosalicylanilide), dibromsalan (DBS, 4',5-dibromosalicylanilide), metabromsalan (MBS, 3,5-dibromosalicylanilide), and 3,3',4,5'-tetrachlorosalicylanilide (TCSA)). The Commissioner has reached the following conclusions and decisions.

SENSITIZATION

1. There were several comments stating or implying that tribromsalan is not a primary photosensitizer and that the cases of photosensitization seen and tested are cross-reactions to 3,3',4,5'-tetracholorsalicylanilide (TCSA), other photosensitizing drugs, natural products, or effects elicited because of intrinsic genetic factors operating in a particular patient. In addition it was stated that the incidence of photosensitization should be established.

The Commissioner concludes that the data in the Panel's report adequately demonstrate that tribromsalan is a primary photosensitizer. Conclusive evidence was set forth by the Panel in its discussion of the Danish experience with a marketed soap in the late 1960's. This soap contained 2 percent tribromsalan rather than the 1 percent often used in this country. After introduction of the product, there were approximately 80 verified cases of photosensitization in patients who had used the product. Of crucial importance is the fact that TCSA was never marketed in Denmark, and therefore cross-photosensitization due to it could not have occurred. The only reasonable explanation of the Danish experience is that tribromsalan acts as a primary photosensitizer.

In addition, the published work of T. Masuda et al., "Contact Dermatitis Due to Hexachlorophene, Irgasen CF3, TCC, TBS, and Diaphene," "Japanese Journal of Dermatology," (Series B), 81:245-248, 1971, documents the primary photosensitization potential of tribromsalan from topical application in humans.

The Commissioner is also aware of the significant hazard of cross-photosensiti-

zation. The Commissioner notes that there are literally thousands of people in this country who are sensitized to TCSA, in most cases, by products such as soap and diaper rinses. Some individuals may have also been sensitized by having been patch tested repeatedly with TCSA. The Commissioner recognizes that it is inescapable and unfortunate that these people, when exposed, will react to tribromsalan and other halogenated salicylanilides. These individuals thus add to the population at risk from exposure to tribromsalan.

The Commissioner therefore concludes that sufficient data are available to demonstrate that tribromsalan is a primary photosensitizer and that there is in addition a significant hazard of tribromsalan due to its cross-sensitization potential. Moreover, although the incidence of photosensitization is not known precisely, it is known to a sufficient degree to permit the conclusion that a hazard exists. Therfore it is not necessary to establish the incidence of photosensitization prior to taking final action on this compound.

2. There was comment that the decrease in photosensitization caused by tribromsalan began when the purified ingredient came onto the market, and when TCSA was no longer used as a positive control for patch testing. The commentator concludes from this fact that tribromsalan is therefore not a primary photosensitizer.

The Commissioner recognizes that because of manufacturing limitations earlier formulations of tribromsalan were contaminated with higher concentrations of photosensitizing chemical impurities, e.g., dibromsalan and metabromsalan, which are more potent sensitizers than tribromsalan. With improved manufacturing techniques, the level of impurities was reduced. The Commissioner agrees that with the availability of a purified compound the incidence of tribromsalan sensitization has been declining, but it has not disappeared. Since tribromsalan is a less potent photosensitizer than the impurities which have been reduced in concentration, the increased purity of tribromsalan may well be an explanation for the observed decline in photosensitization. However, the Panel's data, described above, show that tribromsalan is itself a primary photosensitizer. In addition to the data cited in question 1, published and verified positive reactions to tribromsalan in skin photo-patch tests continued to occur even after TCSA was removed from patch-test kits in the late 1960's. Based upon comment, the Commissioner is also aware that cases of tribromsalan photosensitization occurred up to and even after publication of the Panel's report.

3. Several commentators noted that an expert in photosensitization had pointed out to the Panel that there was indeed a rash of reports of halogenated salicylanilide sensitization in the latter half of the 1960's. The commentators stated that this represented all of the cases the expert had reviewed to that point in time and that recent reports noted that photosensitization was caused by a variety of cross-reactions and predisposing factors. The commentators concluded that halogenated salicylanilides were therefore not primary sensitizers.

When photosensitization to halogenated salicylanilides first become evident in the 1960's, it was frequently recognized and verified by experts working in large dermatologic centers. This resulted in a rash of reports of such cases in the dermatologic literature. As dermatologists became generally aware that antimicrobial bar soaps were a cause of photosensitization, it was no longer a new phenomenon. Hence, they tended not to report additional cases since it did not represent new information and physicians everywhere could identify such cases and recommend that patients stop using the product.

The Panel noted that with the purification of tribromsalan-containing bar soaps the incidence of photosensitization did in fact decline substantially, but it did not decline to zero. The Panel also noted in their report that although the incidence of photosensitization further declined when the major bar soap manufacturers ceased using tribromsalan in their formulations, there were still reported cases of photosensitivity to tribromsalan. The Panel concluded that these cases were not the result of cross-reactions to photopatch testing or due to other predisposing factors. The Commissioner is persuaded by the Panel's argument that even with purification of tribromsalan and modification of photopatch testing techniques, tribromsalan use in bar soaps will result in photosensitization of some individuals.

4. There was comment that the individuals who still react to tribromsalan, either when photopatch tested or when exposed to a tribromsalan-containing product, are members of a small group who are highly active because they are atopic, or they are intrinsically genetically predisposed to be highly reactive.

Absolutely no evidence was submitted to the Commissioner that atopic individuals react to a photosensitizer such as tribromsalan with any higher incidence than the normal population. In fact, there is evidence to the contrary, as reported by Raika in "Studies in Hypersensitivity to Mold and Staphylococci," "Prurigo Besocier, Atopic Dermatitic, Acta Dermato-Venereologica, Stockholm" (1963); Palacias et al. in "Immunological Capabilities of Patients with Atopic Dermatitis," "Journal of Investigational Dermatology," (1966); and Cronin et al. in "Contact Dermatitis in the Atopic," "Acta Dermatovener, Stockholm" (1970).

After a review of the literature, and from the Panel's communications with dermatologists who treat such patients, it is evident to the Commissioner that there is no universal rule that atopic patients are highly reactive to tribromsalan or that they have genetic predisposition to photosensitization. The Commissioner recognizes that there is no dispute that immune reactions are involved in sensitization reactions, including photosensitization. Since the basic mechanism of photosensitization is not fully characterized, some role for intrinsic or genetic factors may eventually be identified.

However, even if there were a segment of the population which is particularly susceptible to harm from a tribromsalan and the other halogenated salicylanilides, the Commissioner concludes that such individuals should not be exposed to these chemicals unless the benefit of their availability outweighs the risk to such persons, or there are no satisfactory substitutes. This is clearly not the case, since safer and equally effective agents are available to the consumer.

5. There was comment suggesting that perhaps all tribromsalan-sensitized patients should be retested by a recognized group of experts in dermatology.

The Commissioner believes that retesting tribromsalan-sensitized patients would serve no useful purpose. The sensitivity of these individuals has already been established by accepted means. To suggest that they resubmit to testing would impose a risk that would not be compensated by any information obtained. The photosensitizing properties of tribromsalan and other halogenated salicylanilides has already been adequately demonstrated in these patients.

6. There was comment that there are no photosensitization reactions reported in the tests performed in guinea pigs, and that this observation means that the Panel's opinion that tribromsalan acts as a primary photosensitizer is unfounded.

The Commissioner recognizes that guinea pigs and their excised skin have been used to screen and study photosensitizing chemicals including tribromsalan, as reported in the book by Herman and Sams, "Soap Photodermatitis: Photosensitivity to Halogenated Salicylanilides" (1972). The guinea pig, as a model for human photosensitization, is a convenient but not a perfect model. It is not unexpected that some materials found negative in the experimental animal model are found to be positive in humans. The contrary situation also exists. Clinical judgment based on evidence from human experience must be given more consideration than evidence from animal models. The Commissioner concludes that evidence of photosensitization potential exists for tribromsalan based on human experience and that observations on guinea pigs, though of scientific interest, do not refute the observations on humans.

7. There was comment that the high levels of tribromsalan used in patch testing do not reflect actual usage levels in OTC products.

It is scientifically rational and common practice in sensitization tests to use procedures that maximize the likelihood of obtaining a reaction and assure induction in those individuals who are reactive. The Commissioner finds that the

levels of tribromsalan used in patch testing are consistent with those used throughout the scientific community for sensitization testing.

8. There was comment that the patch test is an imperfect tool and its use to establish a cause and effect relationship is questionable. The commentator was convinced that in the work of Willis and Kligman, "Diagnosis of Photosensitization Reactions by the Scotch Tape Provocative Patch Test," "Journal of Investigative Dermatology," 51:116–119, 1968, the subjects were exposed to a traumatization, which induced a positive photosensitization test.

The Commissioner agrees that patch testing is an imperfect tool. Nonetheless it has served well in screening for potentially sensitizing materials prior to their use in humans, and has succeeded in identifying previously unknown sensitizing agents for allergic patients. The Commissioner accepts the need for provocative or predictive tests as a means for revealing the existence of moderate sensitizers. Publications by the North American and International Contact Dermatitis Groups have established standards for both induction and elicitation doses in such testing. Using these standards, photosensitivity to the halogenated salicylanilide has been shown. The commentator's contention that traumatization can induce photosensitization by a chemical that is otherwise a nonphotosensitizer is not supported by data and is not accepted by experts in dermatology.

GENERAL TOXICITY

9. There was comment stating that the data submitted to the OTC Antimicrobial I Panel on systemic toxicity testing and percutaneous absorption adequately documents the safety of tribromsalan under the conditions for which it has been used in cleansing products. It was also contended that toxicity of tribromsalan is of the same order of magnitude as other specific ingredients categorized by the Panel in Category III (insufficient information to categorize as generally recognized as safe and effective).

The Commissioner has reviewed the toxicologic data submitted to the Panel. The toxicity profile of tribromsalan indicates toxic effects at high dosage levels. The Commissioner does not agree that the toxicity of tribromsalan is the same order of magnitude as other ingredients classified by the Panel as Category III, which do not have demonstrated photosensitizing properties. While the tribromsalan data showed some similar safety and toxicity data to other ingredients reviewed by the Panel, only the halogenated salicylanilides were recognized as causing photosensitization leading to persistent light reaction.

The Commissioner notes that additional toxicity data are still required as contained in the conclusions of the Antimicrobial I Panel report.

10. Several comments were received concerning the toxicological data for tribromsalan, which had been submitted to the Panel. Several commentators had conducted animal safety tests that failed to produce any abnormalities after 100 days of feeding at 50 mg/kg/day. After feedings with higher doses, the highest amount found in the blood was 2.7 mcg/ml (2.7 parts per million) without any effect on any of the organs examined. They stated that the data showed that topical application to rats failed to produce any brain damage. A research institute reported finding no central nervous system abnormality in the rats tested. There was also comment that no carcinogenic or teratogenic effects were found in an 18-month-multigeneration feeding study in rats.

The Commissioner has again reviewed the data submitted to the Panel and the conclusions included in their report. Toxic effects were seen at high doses in animals, but the entire toxicity profile was not established. The Commissioner notes that the Panel had requested that "effect" and "no-effect" dose information be generated in a single study, but such data either did not exist or were not made available to the Panel.

The data submitted to the Panel help to supply information to complete the toxicological profile for tribromsalan. The Commissioner concludes, however, that even if the complete toxicologic profile became available and showed no toxicity in animals, the risk of photosensitization demonstrated in humans would by itself preclude the use of these halogenated salicylanilides in OTC products.

SAFETY

11. A comment noted that there were very few consumer complaints about tribromsalan-containing soap products even though sales volume was large, and that this fact supports the product's safety.

The Commissioner concludes that the sales record of a product cannot be relied upon solely as proof of safety. There are products such as chloramphenicol, which was extensively tested for safety prior to marketing and others such as hexachlorophene, which was marketed for an extended period without apparent adverse effects, that later proved to cause serious adverse reactions when widely marketed. Therefore, the Commissioner believes that such evidence is not conclusive as to safety, especially with respect to such a complex area as photosensitization. Further, the lack of consumer complaints may also be due to the inability to adequately diagnose adverse reactions or to correlate those reactions with the use of these soap products.

12. There was comment that the consumer complaint index is normally used as evidence for safety of tribromsalan in the market place. One and one-half billion soap bars containing tribromsalan were sold between 1960 and 1974, with a good record of marketing success and a very low consumer complaint index (1 complaint per million soap bars sold), which is comparable to that for nonbacteriostatic bar soaps.

The Commissioner notes that the agency has supported consumer studies that demonstrate that voluntary reports of adverse reactions markedly underestimate the incidence of such reactions. While the consumer complain index may give some indication of the level of adverse reactions, it, like other marketing information, cannot be accepted as definitive evidence of safety in the face of other more pertinent information, discussed above, unequivocally demonstrating a significant hazard. The published literature, as well as communication with dermatologists working in the field of sensitization, documents a number of verified cases of tribromsalan-induced photosensitization, most of which occurred during the period when the products were extensively marketed. The Commissioner noted that apparently not a single one of these patents reported their reaction to the manufacturer of the offending products. A verified case of tribromasalan-induced photosensitization has occurred since the report of the Panel was published.

The Commissioner concludes that many sources of safety information, in addition to the consumer complaint index, should be considered in evaluating the safety of a product.

13. There was comment referring to data on plant-worker health records as evidence for the safety of tribromsalan in the factory and in the marketplace. One commentator stated that it is almost axiomatic that a manufacturer of consumer products will encounter problems associated with a new raw material first among his plant workers exposed to the concentrated agent, rather than in the consumer population which is exposed to a significant dilution of this agent. The same commentator revealed that seminal fluid examination of workers exposed to tribromsalan was normal and that no skin or mucous membrane toxicity was found. It was further noted that plant-worker history of safe contact with tribromsalan must be given serious consideration when it is realized that no special precautions for worker protection were taken, nor have they been found necessary.

The Commissioner agrees that plant-worker health records may have a bearing on the determination of the safety of a product. He is aware of the many documented reports of toxic effects in workers in the asbestos and plastics industry. However, information on the duration of exposure of workers to tribromsalan was not included in the data submitted and is therefore unkown. Other important factors, such as the physical form and concentration of tribromsalan in industrial situations as well as the physical state of tribromsalan required for absorption from body surfaces, are also unknown. For example, the duration of exposure might be inadequate or the concentration might not be within the limits required to induce any sensitization. In addition, a susceptible individual may even develop a tolerance to the product and become immune to its effects.

The Commissioner concludes that the crucial safety problem associated with tribromsalan is its potential for photo-

sensitization. It has been clearly stated in the Panel's report that photosensitization and persistent light reaction are rare events. The true incidence has not been established and probably cannot be accurately estimated. However, the Commissioner notes that primary photosensitization is not common and it is very unlikely that the small number of exposed employees, either at the plant of the manufacturer or formulator, would provide a population large enough to include an individual, on a statistical probability basis, who would be sensitive to tribromsalan. In addition, it is not clear whether the state of industrial hygiene in chemical plants was adequate to protect against the kind of exposure required for inducing sensitization.

The Commissioner is of the opinion that with regard to the seminal fluid examination of workers, interpretation of sperm count data is difficult at best. He notes that the number of samples was low and the range of values great. Interpretation of safety from this fragmentary data is difficult, if not impossible.

The Commissioner concludes that there are no data sufficient to make an objective judgment based on exposed workers.

GENERAL COMMENTS

14. One commentator took issue with the classification of all halogenated salicylanilides into one group with respect to safety.

The Commissioner has confined the proposal to four halogenated salicylanilides: Tribromsalan (TBS, 3,4',5-tribromosalicylanilide), dibromsalan (DBS, 4',5-dibromosalicylanilide), metabromsalan (MBS 3,5-dibromosalicylanilide), and 3,3',4,5' - tetrachlorosalicylanilide (TC SA). Herman and Sams, recognized experts in sensitization, entitled their book, "Soap Photodermatitis: Photosensitivity to Halogenated Salicylanilides," and have stated that all salicylanilides containing certain structural requirements have a potential for photosensitization. However, the Commissioner will insist that any halogenated salicylanilide proposed for future OTC topical use be adequately tested for photosensitization potential prior to use in humans.

15. There was comment regarding a test in which a marketed bar soap containing no antimicrobial ingredients was used and found to be irritating. The commentator noted that the Food and Drug Administration had not removed the soap from the market.

The Commissioner notes that the reaction reported in users of the marketed soap is well known and is a simple irritation reaction probably resulting from the high alkalinity of the product. This irritation is mild and is known to disappear when contact stops. On the other hand, photosensitization with halogenated salicylanilides is much more severe and may lead to persistent light reactions lasting months, years or even a lifetime. The Commissioner finds that the latter obviously represents a significant hazard while the former does not.

16. One commentator stated that the individual nonproprietary names, 4',5-dibromosalicylanilide or dibromsalan and 3,5-dibromosalicylanilide or metabromsalan, be used rather than the incorrect "dibromsalans" when the Panel means "dibrominated" salicylanilides.

The Commissioner concurs with the statement of the commentator. The Food and Drug Administration and other government agencies regularly use these names officially; they are accepted United States Adopted Names (USAN). Accordingly, the nomenclature has been revised to clarify 4',5-dibromosalicylanilide as dibromsalan (DBS) and 3,5-dibromosalicylanilide as metabromsalan (MBS).

17. There was comment that there is a demand in the marketplace for antimicrobial agents, and the obvious result of banning tribromsalan will be an increase in the use of less well-proven antimicrobial agents.

The Commissioner notes the Panel made it clear in their discussion of several ingredients they categorized as Category III (insufficient information upon which to determine general recognition of safety and effectiveness) that general recognition of safety and effectiveness was attainable if certain further testing were successfully carried out; the Commissioner accepts this position.

The Commissioner concludes that those ingredients in Category III have a much better history of safety than tribromsalan and would not result in exposing the American public to a health hazard equal to that created by the use of tribromsalan, nor does it result in the increased use of less well-proven antimicrobial ingredients. The purpose of the review of OTC drug products is to assure that the ingredients are safe and effective.

18. A comment was made that marketing many different antimicrobial ingredients assures that individuals have a decreased body burden for any one antimicrobial chemical. The implication of this remark is that access to a variety of antimicrobials reduces the potential of an individual consumer to be exposed to a toxic burden of a single antimicrobial compound.

The Commissioner concludes that the existence of a number of antimicrobial products does not reduce risks inherent in the toxicity of a single product because a consumer may use only one product. The theoretical advantage of avoiding large concentrations of any one product through use of many different products is far outweighed by the ability of tribromsalan and the other halogenated salicylanilides to cause severe photosensitization reactions. Only if all antimicrobials had the same toxicity profile would the stated conclusion of the commentator have validity. Because of these considerations, the comment cannot be viewed as a basis for modifying the recommendations of the Panel on tribromsalan.

On the basis of the Panel's report, the documented evidence of photosensitization and cross-photosensitization caused by these halogenated salicylanilides, the lack of toxicological data adequate to establish a safe level for use, the availability of other safer agents, the adverse benefit-to-risk ratio, and the foregoing comments, the Commissioner concludes that these halogenated salicylanilides, including tribromsalan, dibromsalan, metabromsalan, and tetrachlorosalicylanilide, cannot be considered generally recognized as safe for any use in drug and cosmetic products. Therefore, the Commissioner has determined 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 (21 U.S.C. 321(p)) for which an approved new drug application pursuant to section 505 (21 U.S.C. 355) of the act and 21 CFR Part 314 is required. The Commissioner has also determined that these halogenated salicylanilides are deleterious substances that 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 shall be deemed to be adulterated under section 601(a) of the act.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 601(a), 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 361(a), 371)) and the Administrative Procedure Act (secs. 4, 5, 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)) and under authority delegated to the Commissioner (21 CFR 2.120), Chapter I of Title 21 of the Code of Federal Regulations is amended as follows:

1. In Part 310, 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-tribromosalicylanilide), dibromsalan (DBS, 4',5-dibromosalicylanilide), metabromsalan (MBS, 3,5-dibromosalicylanilide), and 3,3',4,5' - tetrachlorosalicylanilide (TC-SA)) 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 product 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 initially introduced into interstate commerce after December 1, 1975, that is not in compliance with this section is subject to regulatory action.

2. In Part 700, 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), dibromalan (DBS,4',5-dibromosalicylanilide, metabromsalan (MBS, 3,5-dibromosalicylanilide) and 3,3',4,5' - tetrachlorosalicylanilide (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 halogented 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 initially introduced into interstate commerce after December 1, 1975, that is not in compliance with this section is subject to regulatory action.

Effective date. This regulation shall be effective on December 1, 1975.

(Secs. 201, 502, 505, 601(a), 701, Pub. L. 717, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 361(a), 371); (5 U.S.C. 553, 554, 702, 703, 704))

Dated: October 22, 1975.

SHERWIN GARDNER,
Deputy Commissioner of Food and Drugs.

[FR Doc.75-29094 Filed 10-29-75;8:45 am]

Title 24—Housing and Urban Development

CHAPTER V—OFFICE OF ASSISTANT SECRETARY FOR COMMUNITY PLANNING AND DEVELOPMENT, DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

[Docket No. R-75-292]

PART 570—COMMUNITY DEVELOPMENT BLOCK GRANTS

Submission of Applications

On February 7, 1975, in 40 FR 5952, the Department amended Title 24 of the Code of Federal Regulations by adding Subpart E—Applications and Criteria for Discretionary Grants to Part 570 of Chapter V. On June 9, 1975, at 40 FR 24692, the Department revised 24 CFR Part 570 to consolidate the several changes previously made to the above part, including the above Subpart E. Effective July 22, 1975, the deadline for applicants to submit final applications for general purpose funds for metropolitan areas was changed from May 15, 1975, to September 30, 1975. The Department is extending the September 30, 1975, deadline for certain communities to November 30, 1975.

The additional time is necessary to enable these communities to complete, revise, or update their applications to include new priorities and needs brought on as a result of Federally recognized disasters.

Except for the extension of the deadline for receipt of final applications to November 30, 1975 the regulations governing discretionary grants remain unchanged and are applicable.

It is necessary that this amendment taken effect at the earliest possible date so that applicants unable to meet the previously established deadline can plan the completion of their applications within the time remaining under the extended date. Accordingly, the Assistant Secretary for Community Planning and Development finds good cause for foregoing the usual public comment and notice procedure, and he further finds good cause that this amendment to the regulations should take effect on the date of publication.

In connection with the environmental review of this technical change to the final regulations, a Finding of Inapplicability has been made under HUD Handbook 1390.1, 38 FR 19182. A copy of the Finding is available for public inspection in the Office of the Rules Docket Clerk, Office of the General Counsel, Room 10245, Department of Housing and Urban Development, 451–7th Street, SW., Washington, D.C. 20410.

It is hereby certified that the economic and inflationary impacts of these amendments have been carefully evaluated in accordance with OMB Circular No. A-107.

In view of the foregoing, 24 CFR Part 570 is amended by revising § 570.400(c)(3)(i)(A) to read as follows:

§ 570.400 General.

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(c) * * *
(3) * * *
(i) * * *

(A) For metropolitan areas—March 15, 1975 through September 30, 1975; except for certain communities which had filed preapplications for assistance under this part and had been invited by HUD to submit full applications but were unable to complete the application because of the occurence of Federally recognized disasters, for which the deadline is extended to November 30, 1975.

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(Title I of the Housing and Community Development Act of 1974 (Pub. L. 93-383); and sec. 7(d), Department of Housing and Urban Development Act (42 U.S.C. 3535(d))

Effective date. This amendment shall be effective on October 30, 1975.

WARREN H. BUTLER,
Deputy Assistant Secretary for Community Planning and Development.

[FR Doc.75-29167 Filed 10-29-75;8:45 am]

CHAPTER VIII—LOW INCOME HOUSING, DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

[Docket No. R-75-334]

PART 811—FINANCING

Tax Exemption of Obligations of Public Housing

The Department is amending Title 24 by adopting a new Part 811—Financing, and new Subpart A—Tax Exemption of Obligations of Public Housing Agencies Under Section 11(b) of the Act. Subpart A implements, in accordance with section 201(b) of the Housing and Community Development Act of 1974 (42 USC 1437, note), section 11(b) of the United States Housing Act of 1937 (42 USC 1437i) and section 3(6) of the 1937 Act (42 USC 1437a) in relation thereto, both of which sections were incorporated into the Act by section 201 of the Housing and Community Development Act of 1974. (Section 3(6) defines the term "public housing agency" and section 11(b) authorizes tax exemption of obligations issued by a public housing agency in connection with a low-income housing project assisted under the Act.) The Subpart further sets forth requirements and procedures for HUD approval of applicants and applications for tax exemption under section 11(b).

The Department invited interested persons to submit comments on the Interim Rule in which form this amendment was first published on May 27, 1975 at 40 FR 22829. The principal recommendations made by those comments have been incorporated in this amendment: (1) The regulation provides specifically that it applies only to tax exemption sought under section 11(b) of the Act and not to any other tax exemption provision of law or Government regulations and (2) the regulation provides that a reserve equal to one year's debt service may be established out of the proceeds of the obligations.

An additional comment recommended that no limit be placed on the amount or the type of reserve fund so as to allow maximum freedom to local public housing agencies in developing security devices with reserve funds; or that the provisions of Proposed Treasury Regulation 1.103-14-(b) with respect to reserves be adopted. The recommendation that there be no limit was rejected because without such a limit the regulation would fail to prevent the abuses of arbitrage financing under the United States Housing Act of 1937. As to the adoption of the Treasury Regulation reserve policy, it is the De-