**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**21 CFR Parts 310 and 333**

**[Docket No. 80N-0476]**

**RIN 0905-AA06**

## Topical Antifungal Drug Products for Over-the-Counter Human Use; Tentative Final Monograph

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice of proposed rulemaking.

**SUMMARY:** The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) topical antifungal drug products are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Antimicrobial II Drug Products and public comments 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 March 12, 1990. Because of the length and complexity of this proposed regulation, the agency is allowing a period of 120 days for comments and objections instead of the normal 60 days. New data by December 12, 1990. Comments on the new data by February 12, 1991. Written comments on the agency's economic impact determination by March 12, 1990.

**ADDRESSES:** Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, Room 4-62, 5600 Fishers Lane, Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:** William E. Gilbertson, Center for Drug Evaluation and Research (HFD-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

**SUPPLEMENTARY INFORMATION:** In the **Federal Register** of March 23, 1982 (47 FR 12480), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC topical antifungal drug products, together with the recommendations of the Advisory Review Panel on OTC Antimicrobial II 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 June 21, 1982. Reply comments in response to comments filed in the initial comment period could be submitted by July 21, 1982.

In a notice published in the **Federal Register** of September 7,1982 (47 FR 39464), the agency advised that it had reopened the administrative record for OTC topical antifungal drug products as it pertains to products used for the treatment of diaper rash to allow consideration of the statement of the Advisory Review Panel on OTC Miscellaneous External Drug Products on these products. Interested persons were invited to submit comments until December 6, 1982. Reply comments in response to comments filed in the initial comment period could be submitted until January 5, 1983. In response to numerous requests, the agency issued a notice in the **Federal Register** of December 28, 1982 (47 FR 57738) granting an extension of the deadline for comments until February 4, 1983, and for reply comments until March 7, 1983.

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 (address above), after deletion of a small amount of trade secret information. Data and information received after the administrative record was reopened have also been put on display in the Dockets Management Branch.

In response to the advance notice of proposed rulemaking, nine drug manufacturers, one drug manufacturers' association, two medical facilities, and three consumers submitted comments. In response to the reopening of the administrative record to include OTC diaper rash drug products, four drug manufacturers, one manufacturer of fiber products, and one drug manufacturers' association submitted comments. Copies of the comments received are on public display in the Dockets Management Branch.

The advance notice of proposed rulemaking, which was published in the **Federal Register** of March 23, 1982 (47 FR 12480), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the present document is designated in the OTC drug review regulations as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule) to add new subpart C to part 333 (proposed in the **Federal Register** of July 9, 1982; 47 FR 29986), FDA states for the first time its position on the establishment of a monograph for OTC topical antifungal drug products. In this tentative final monograph the agency is also proposing to amend part 310. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC topical antifungal drug products.

This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC topical antifungal drug products as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them.

The OTC drug procedural regulations (21 CFR 330.10) now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, 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 monograph stage, but will use instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the **Federal Register**. On or after that date, no OTC drug product that is subject to the monograph and that contains a

nonmonograph condition, i.e., a condition that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. Further, any OTC drug product subject to this monograph that is repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In the advance notice of proposed rulemaking for OTC topical antifungal drug products (47 FR 12480), the agency suggested that the conditions included in the monograph (Category I) be effective 6 months after the date of publication of the final monograph in the **Federal Register**. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 6 months after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products may have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and if further reformulation is required, there could be a further delay in having a new product available for manufacture.

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss, but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the **Federal Register**. The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and reformulate their products and have them in compliance in the marketplace.

If the agency determines that any labeling for a condition included in the final monograph should be implemented sooner than the 12-month effective date, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for data notice published in the **Federal Register** of December 16, 1972 (37 FR 26842) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch (address above).

## I. The Agency's Tentative Conclusions on the Comments and Reply Comments

### *A. General Comments*

1. Two comments contended that OTC drug monographs are interpretive, as opposed to substantive, regulations. The comments referred to statements on this issue submitted earlier to other OTC drug rulemaking proceedings.

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products, published in the **Federal Register** of May 11, 1972 (37 FR 9464) and in paragraph 3 of the preamble to the tentative final monograph for antacid drug products, published in the **Federal Register** of November 12, 1973 (38 FR 31260). FDA reaffirms the conclusions stated there. Court decisions have confirmed the agency's authority to issue substantive regulations by rulemaking. (See, e.g., *National Nutritional Foods Association* v. *Weinberger*, 512 F.2d 688, 696–98 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers* v. *FDA*, 487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd*, 637 F.2d 887 (2d Cir. 1981).)

2. One comment requested that a currently marketed OTC spray-on antifungal foot powder be removed from the market immediately because, despite the warning on the container label not to breathe the spray, use of this product results in unavoidable inhalation. The comment maintained that the dispenser is defective in design because the spray cannot be localized to the toe area but envelops the head as well.

The OTC drug review program establishes monograph conditions under which OTC drug products are generally recognized as safe and effective and are appropriately labeled. These conditions principally consist of acceptable ingredients and approved labeling such as indications for use, warnings, and directions. Other agency regulations require warnings for certain drugs in dispensers pressurized by gaseous propellants. (See 21 CFR 369.21.) These warnings are intended to alert consumers to minimize contact of the aerosolized product with the eye and to minimize inhalation of the aerosol.

The agency continually monitors adverse reaction reports. When safety problems arise from the use of a particular ingredient or dosage form, such as an aerosol, the agency takes appropriate action. For example, in the **Federal Register** of August 16, 1977 (42 FR 41374), the agency issued a final regulation declaring that any aerosol drug or cosmetic product containing zirconium is a new drug or an adulterated cosmetic. This action was prompted by the agency's concern about the inhalation of zirconium aerosol by consumers. FDA was aware of reports that zirconium compounds caused skin granulomas and toxic effects in the lungs and other organs of laboratory animals. The regulation was intended to keep zirconium-containing aerosols off the market until adequate safety testing had been completed.

The agency has reviewed the submissions made to the Panel and other data to determine whether there have been adverse reaction reports or potential safety problems reported from inhalation of the product mentioned by the comment. None have been found. Accordingly, the agency considers the label warnings for this product to be adequate, and finds that there is no basis for removing it from the market. The agency also notes that antifungal drug products are available in dosage forms other than aerosols, such as creams, lotions, and powders. Consumers who find aerosols objectionable may select a different dosage form.

3. One comment suggested revisions of several discussions in the Panel's report. These suggestions included expansion or clarification of narrative statements related to sites of infection, fungal cultures, effectiveness criteria, sample size, and indications for a specific ingredient.

The Panel's report represents the Panel's opinion and recommendations based on clinical experience, a review of the scientific literature, and an evaluation of the data presented to it. As stated above, the present tentative

final monograph represents FDA's adoption of the Panel report together with necessary modifications. This document is not, however, a restatement of the Panel report. And, because the revisions suggested by the comment would not alter the tentative final monograph, it is not necessary to address specifically the suggested revisions to the Panel's report as they relate to the form of the report.

4. One comment objected to a television advertisement which claimed that, according to an expert medical panel report to the FDA, a tolnaftate product contains the only medication proven to prevent reinfection from athlete's foot fungus and also "conveyed the message * * * that tolnaftate prevents jock itch." The comment stated that tolnaftate has not been approved for the prevention of jock itch and that "these advertising claims show dramatically the adverse consequences that would ensue if special prophylactic studies were to be required for agents that have already been proven effective in the treatment of fungal infections and if at the same time these requirements were not applied consistently to all drugs." The comment requested that FDA recognize that effective antifungals such as the undecylenates prevent reinfection and that separate prophylaxis studies are not necessary; that studies by Sulzberger et al. demonstrate the prophylactic effect of the undecylenates; and that if prophylaxis studies are to be required, they should be uniformly required of all drugs.

A reply comment responded that the primary regulatory jurisdiction for OTC drug advertising rests with the Federal Trade Commission (FTC), not FDA. The reply comment went on to state that the comment made several misstatements of facts and pointed out that the athlete's foot commercial did not make any claim for use of tolnaftate to prevent jock itch but contained the truthful claim in a tagline that the tolnaftate product for jock itch "cures jock itch fast" and that such a claim is clearly a treatment rather than a prevention claim. The reply comment further asserted that the Panel clearly listed tolnaftate as the only antifungal agent that has been demonstrated to be effective in preventing athlete's foot infection. The comment added that advertising that properly references the OTC drug review process has been commonplace in OTC drug advertising for many years and concluded that it could not understand how the truthful advertising statements could possibly "show dramatically the adverse consequences * * *."

The agency agrees with the reply comment that FTC has the primary responsibility for regulating OTC drug advertising and recommends that concerns about the truthfulness of advertising claims or implications be referred to the FTC. Resolution of the truthfulness of the advertisement in question is outside the scope of the OTC drug review. For a discussion of the Sulzberger study and the effectiveness of undecylenates in preventing reinfection and the need for separate prophylaxis studies, see comment 20 below.

5. In response to the reopening of the administrative record for OTC topical antifungal drug products to include the statement on diaper rash by the Advisory Review Panel on OTC Miscellaneous External Drug Products (47 FR 39464), two comments requested that a separate rulemaking be established for OTC drug products that prevent and treat diaper rash. One of the comments suggested that if a separate monograph is not established, a clearly identifiable subsection of the monograph for OTC skin protectants would be appropriate for diaper rash drug products. The comment argued that in cases where the ingredients in OTC diaper rash drug products are not skin protectants, these ingredients could be handled under appropriate combination policies. Another comment mentioned that several of the ingredients listed by the agency as diaper rash ingredients had not been referred to any rulemaking and suggested that these ingredients, especially those which are barrier-like skin protectants (e.g., cod liver oil, talc), should be referred to the rulemaking on OTC skin protectant drug products.

One comment concerned the use of zinc oxide for treatment of diaper rash. Another comment requested that its earlier submissions on sodium bicarbonate be included in the administrative record for a proposed monograph on OTC drug products for the treatment of diaper rash. The comments included articles on various uses of sodium bicarbonate and excerpts of a marketing study on this ingredient (Ref. 1). One comment stated that a review of ingredients in diaper rash product submissions revealed the use of borax in one product and boric acid in four products in concentrations ranging from 0.5 to 7.14 percent. The comment noted that according to the definition of "active ingredient" in § 210.3(b)(7) (21 CFR 210.3(b)(7)), boric acid and borax are not present as active ingredients but as buffering agents (i.e., pharmaceutical necessities).

One comment suggested two tests for the agency to consider as standards by which the effectiveness of a diaper rash product may be determined for a claimed therapeutic benefit. One comment expressed its opposition "to the inclusion in the OTC monographs of any anecdotal or superfluous comments about disposable diapers that are not confirmed by scientific data."

The agency has determined that it would be more appropriate to address the entire issue of diaper rash prevention and treatment at one time, either in a separate rulemaking or concurrently in each respective rulemaking. Accordingly, the comments on diaper rash drug products submitted to the rulemaking on antifungal drug products will be considered at a later time. An antifungal ingredient that is determined to be appropriate for the relief of diaper rash will be included in the appropriate tentative final monograph applicable to OTC diaper rash drug products. The same antifungal ingredient also may be determined to be appropriate for use in athlete's foot, ringworm, and jock itch and, therefore, can remain in this rulemaking for OTC antifungal drug products.

### *B. Comment on Definitions*

6. Referring to the definition of dermatophyte in § 333.203(d) of the Panel's recommended monograph (47 FR 12480 at 12564), one comment pointed out that the definition should be revised to state that "filamentous fungi are *saprophytic* on human skin, hair or nails, (dead tissue only) and are *not* parasitic."

In its report the Panel discussed dermatophytes as follows:

> Dermatophytes. A group of taxonomically related fungi which normally live in soil, where they metabolically decompose organic keratinous debris through the enzymatic digestion of keratin (a fibrous protein also found in cornified epidermis). Many of these fungi cause superficial skin infections including athlete's foot, jock itch, and ringworm in humans and in animals by invading and living in the cornified epidermis or in the hair or nails. These fungi are subdivided and classified according to their usual source of isolation from soil, from animals, or from man.
>
> The dermatophytic fungi most commonly mentioned in this document include *Trichophyton rubrum (T. rubrum), Trichophyton mentagrophytes (T. mentagrophytes),* and *Epidermophyton floccosum (E. floccosum).* These organisms are the most frequent causes of human infections in the United States, but other strains may be involved. (See 47 FR 12480 at 12485.)

The Panel's definition of dermatophyte in § 333.203(d) i.e., "a fungus that is parasitic upon the skin, hair, or nails of humans or animals," was based on the above discussion. Words such as "parasitic" and "saprophytic," both of which may be applicable to fungi, have scientific definitions that are not generally understood by laymen and thus require further definition in order to be understood. Therefore, to make the term dermatophyte more understandable to laymen, the agency has deleted the word "parasitic" from its definition and is proposing the following definition in this tentative final monograph: *"Dermatophyte.* A fungus that invades and lives upon the skin or in the hair or nails." This definition is abstracted from the Panel's discussion, does not include any words that need further definition, and is sufficiently clear for use in this tentative final monograph. The Panel's reference to "animal" has been deleted from the definition because this rulemaking concerns only drugs intended for OTC human use.

*C. Comment on Chloroxylenol*

7. In response to the Panel's recommendation that one double-blind, placebo-controlled clinical trial be conducted to establish the effectiveness of chloroxylenol, one comment submitted such a study (Ref. 1) and stated its belief that the results will enable chloroxylenol to be moved from Category III to Category I. The comment also submitted three additional studies (Refs. 2, 3, and 4) containing safety data in response to the agency's concern (Ref. 5) about the irritation/sensitization potential of 2 percent chloroxylenol. The comment concluded that all of these studies demonstrate that a product containing 2 percent chloroxylenol is safe for human use against fungal infections.

The Panel concluded that chloroxylenol for OTC topical antifungal use is safe for application to small areas of the skin over short periods of time, at least over a 13-week period, but that there were insufficient efficacy data available to permit final classification (47 FR 12480 at 12533). The study submitted by the comment was a double-blind controlled trial (Ref. 1) in which 2 percent chloroxylenol (vehicle not specified) was compared with its aqueous emollient base vehicle in the treatment of postassium hydroxide (KOH) positive, culture positive tinea pedis. The patients were treated twice a day for 28 days and evaluated at time 0 (entry into the study) and at 14, 28, and 42 days (no therapy for 2 weeks before the last evaluation). In order for a patient to be considered cured, the patient must have had neither signs nor symptoms of active fungal infection in addition to a negative KOH and a negative culture at both the 28-day and 42-day evaluations. Of the 53 subjects who completed the study, 9 were changed to the active drug after initially being on the placebo. Four of the nine were changed to the active products after 3 to 14 days of placebo therapy. Five of the nine were changed to the active drug after 28 days of placebo therapy. The latter five cases were counted as placebo failures in the statistical analysis. When changed to the active drug, they were treated as new cases. Thus, 39 patients were treated with 2 percent chloroxylenol, and 33 were considered cured (92.3 percent). Nineteen patients were treated with placebo, and only three were considered cured (15.8 percent).

The agency has some concerns about this study. Of the 53 patients cultured, 46 yielded *Trichophyton tonsurans (T. tonsurans).* Although *T. tonsurans* is becoming a more common pathogen on the body and produces almost all of the scalp ringworm seen in the United States, it remains uncommon to find this pathogen on the feet. A published study indicates that only 5 to 15 percent of pedal lesions yield. *T. tonsurans* (Ref. 6). Consequently, it was most unusual for the submitted study to find 46 of 53 (86.8 percent) of the fungal isolates yielding this organism from the feet. It is not known whether chloroxylenol or other antifungals are as active against *T. tonsurans* as they are against the most common organisms cultured in athlete's foot. Only a very few patients in this study had the fungi *Trichophyton rubrum (T. rubrum), Trichophyton mentagrophytes (T. mentagrophytes),* or *Epidermophyton floccosum (E. floccosum),* and none were reported to have *Mricrosporum canis (M. canis)* or *Candida albicans (C. albicans).* The Panel stated that when establishing antifungal activity the antifungal action of the specific ingredient must be tested using all these fungi (47 FR 12480 at 12561).

This study is also flawed by inadequate documentation of the randomization procedure, a low proportion of evaluable patients, and a mistaken classification of patient outcomes. Also, patients were allowed to switch therapy during the trial. This shifting of patients between treatment groups not only interfered with the randomization process, but also jeopardized the double-blind nature of the study. In view of these problems, the comment's analysis and claim of drug efficacy based on data from 53 patients (5 entered twice) has questionable validity.

After the patient outcome data were corrected and reclassified, there were nine patients with unknown outcomes due to incomplete followup data (less than 4 weeks) on placebo. Consequently, out of 85 patients who entered the study, there were only 44 patients with evaluable data. There is no assurance that the treatment groups are still comparable after nearly half of the patients were excluded from the analysis. Thus, even if the randomization procedure had been adequate and data following drug reassignment are disregarded, this study does not provide sound statistical evidence that 2 percent chloroxylenol is effective for the treatment of athlete's foot. Consequently, the agency concludes at this time that chloroxylenol should not be reclassified as Category I for the treatment of athlete's foot because the data submitted are inadequate to show effectiveness.

Although noting that some cases of minor irritation had been reported, the Panel concluded that chloroxylenol in concentrations of 3.75 percent or less is safe for OTC antifungal use in the treatment of athlete's foot, jock itch, or ringworm. Nevertheless, the agency expressed concern that if chloroxylenol is irritating it could cause severe dermatitis on areas other than the feet, such as the groin, and recommended standard irritation and sensitization tests on the formulations being marketed to determine whether a warning against use on areas other than the feet would be needed (Ref. 5). In response to the agency's concern, the comment submitted primary skin irritation and primary eye irritation studies on rabbits (Refs. 2 and 3). In the skin irritation study, the test material was applied to 18 intact and 18 abraded sites on rabbits' backs, covered for 24 hours, and evaluated. The highest Draize score on any site was a 2, and all redness was gone by 48 hours. Thus, the product was classified as nonirritating. The standard Draize primary eye irritation study also indicated that the product was nonirritating. The agency has reviewed these studies and concurs with the comment that 2 percent chloroxylenol was shown to be nonirritating.

The comment also submitted two human studies. One study used a repeated insult patch test with a formulation containing 2 percent chloroxylenol (Ref. 4). Ten subjects were treated in the groin area using a modified Draize-Schelanski test. The

area was covered for 24 hours following each application, rested for 24 hours, and then applications were repeated for a total of 10 times. Following a 14-day rest period, a challenge application was made to the same area. There were no adverse reactions, indicating a lack of irritation or sensitization. In the second human study, the efficacy study discussed above (Ref. 1), in which 39 subjects with athlete's foot were treated with the 2-percent chloroxylenol product, there were no adverse reactions, the regenerated tissue was good, and subject acceptance of the product was very good.

The agency concludes that these data indicate that 2 percent chloroxylenol does not appear to have a potential for irritation or sensitization and, therefore, can be considered safe for topical use on all areas of the body. In addition, the agency agrees with the Panel that 3.75 percent or less chloroxylenol is safe for use in the treatment of athlete's foot, jock itch, or ringworm over short periods of time, at least over a 13-week period.

In conclusion, safety appears to have been adequately demonstrated, but there is insufficient evidence of effectiveness to reclassify 2 percent chloroxylenol to Category I as an OTC antifungal agent for use in the treatment of athlete's foot, jock itch, and ringworm. The agency's detailed comments and evaluations are on file in the Docket's Management Branch (Ref. 7).

**References**

(1) Tilton, R.C., and R.E. Pinkerton, "A Controlled Clinical Study to Evaluate the Effectiveness of Chloroxylenol for the Treatment of Tinea Pedis," unpublished study in Comment No. LET011, Docket No. 80N–0476, Dockets Management Branch.

(2) Fanaras, J.C., and M. Schmidt, "Primary Skin Irritation Evaluation of Absorbine Athlete's Foot Product (L) 2119A," unpublished study in Comment No. LET010, Docket No. 80N–0476, Dockets Management Branch.

(3) Fanaras, J. C., and M. Schmidt, "Primary Eye Irritation Evaluation of Absorbine Athlete's Foot Product (L) 2119A," unpublished study in Comment No. LET010, Docket No. 80N–0476, Dockets Management Branch.

(4) Pinkerton, R. E., "Chloroxylenol Repeated Insult Patch Test in Human Subjects," unpublished study in Comment No. LET010, Docket No. 80N–0476, Dockets Management Branch.

(5) Letter from W. E. Gilbertson, FDA, to D. R. Smith, W. F. Young, Inc., coded LET007, Docket No. 80N–0476, Dockets Management Branch.

(6) Bronson, D. M., et al., "An Epidemic of Infection with *Trichophyton Tonsurans* Revealed in a 20-year Survey of Fungal Infections in Chicago," *Journal of the American Academy of Dermatology*, 8:322–330, 1983.

(7) Letter from W. E. Gilbertson, FDA, to D. R. Smith, W. F. Young, Inc., Coded LET014, Docket No. 80N–0476, Dockets Management Branch.

*D. Comments on Clioquinol*

8. One comment requested that clioquinol (iodochlorhydroxyquin) (alone or in combination with hydrocortisone) be added to the Panel's list of drugs effective in the treatment of candidal infections (cutaneous candidiasis). The comment cited four studies in support of clioquinol's effectiveness for this use (Refs. 1 through 4).

The combination of clioquinol and hydrocortisone is discussed in comment 23 below. In this comment the agency is presenting its review of the four studies submitted by the comment and its determination that the data are inadequate to establish the effectiveness of clioquinol when used alone in the treatment of cutaneous candidiasis.

In a study by Brecker et al. (Ref. 1), a patient group (unidentified with respect to sex) was diagnosed as having moniliasis. The treatment sites were the following: axilla, buttocks, groin, genitalia, perianal area, and perineal area. Only 32 patients out of the 354 culture-verified patients were shown to have infections caused by *Candida albicans*, and only 7 of these patients were treated with the single ingredient clioquinol. Other patients were treated with a combination of clioquinol and hydrocortisone, hydrocortisone alone, and the vehicle alone. Therefore, as stated by the authors themselves, the number of patients in the clioquinol treatment group was too small to make the results statistically significant.

Carpenter et al. (Ref. 2) tested the same four components in 112 female patients diagnosed as having secondary bacterial or fungal infections. The study analyzed data from only those patients having organisms of accepted pathogenicity: Coagulase positive *Staphylococcus aureus, Candida albicans, Candida tropicalis, Microsporum gypseum, Microsporum canis, Trichophyton rubrum, Trichophyton mentagrophytes*, and mixed *Staphylococcus aureus* and fungal infections. However, the distribution of the infections caused by these organisms in the treatment populations was not specified. Therefore, this study provides no specific data on the activity of clioquinol as a single ingredient in infections caused by *Candida*.

The study by Abdel-Aal et al. (Ref. 3) was not designed to demonstrate the effectiveness of clioquinol as a single ingredient and therefore does not provide any useful information relative to the activity of clioquinol in the treatment of cutaneous candidiasis.

The study of Barba-Rubio (Ref. 4), designed in the same manner as the Abdel-Aal study, also did not provide any useful data on the activity of clioquinol used alone in the treatment of cutaneous candidiasis.

In summary, the four studies cited by the comment did not demonstrate the effectiveness of clioquinol as a single ingredient in the treatment of cutaneous candidiasis. Further, in the preamble of the advance notice of proposed rulemaking, the agency dissented from the Panel's recommendation that OTC antifungal drug products be labeled for the "treatment of superficial skin infections caused by yeast (*Candida*)" (47 FR 12480). The agency solicited comments on the Panel's recommendations that haloprogin, miconazole nitrate, and nystatin be available OTC for the treatment of candidal infections. Except for the comments received on the use of those drugs for external feminine itching associated with vaginal yeast (*Candida*) infection, no comments were received. Therefore, the agency reaffirms its position that no antifungal ingredient can be labeled for OTC use for the treatment of cutaneous candidiasis. However, based on the Panel's Category I recommendations, the agency finds this claim to be a valid professional labeling claim and, therefore, is moving the Panel's recommended labeling in § 333.250(b)(4) to the professional labeling section of this tentative final monograph. This professional labeling approach is appropriate for haloprogin and miconazole nitrate because these ingredients have other appropriate OTC antifungal claims, but is not appropriate for nystatin, which currently does not have any OTC labeling claims and remains a prescription drug. As discussed in comment 35 below, the agency is deferring consideration of the use of antifungal ingredients for external vaginal itching associated with vaginal yeast (*Candida*) infection to the rulemaking for OTC vaginal drug products.

**References**

(1) Brecker, L. J., et al., "Protocol #02," draft of unpublished paper in OTC Volume 070193.

(2) Carpenter, C. L., et al., "Combined Steroid Antiinfective Topical Therapy in Common Dermatoses: A Double-Blind, Multi-Center Study of Iodochlorhydroxyquin-Hydrocortisone in 277 Patients," *Current Therapeutic Research*, 15:650–659, 1973.

(3) Abdel-Aal, H., et al., "A Double-Blind Comparison of a New Combination (Halcinonide-Neomycin-Amphotericin) and Active Controls in Cutaneous Candidiasis and Steroid-Responsive Dermatoses," *The Journal of International Medical Research*, 4:232–236, 1976.

(4) Barba-Rubio, J., "Clinical Evaluation of a New Halcinonide-Antifungal Combination," *Current Therapeutic Research*, 20:655–660, 1976.

9. One comment stated that the Panel made several errors in its review of antibacterial data submitted for clioquinol (Refs. 1 and 2) and that these errors resulted in the Panel's conclusion that clioquinol has little or no antibacterial activity (47 FR 12480 at 12497). The comment submitted an analysis that addressed each of the errors it claimed the Panel made in reviewing the submitted data.

One point noted by the comment in its analysis was that in discussing the submitted in vitro data the Panel stated that "soybean-casein digest agar was used, although Mueller-Hinton is the standard medium" (47 FR 12496). The comment pointed out that trypticase soy agar (BBL) is a general purpose nutrient medium that is also used for sensitivity testing, such as minimal inhibitory concentration (MIC) determination. The comment added that Mueller-Hinton agar is the accepted standard medium for the Standardized Disc Agar Diffusion Assay; but that because the studies reported were not being correlated with disc zone sizes, any suitable growth medium was acceptable for the MIC determination.

The comment also stated that the Panel's assessment of the MIC for the tested organisms (47 FR 12496 to 12497) is incorrect because the Panel misread the table that summarized the results of the MIC determination; that the values recorded in the table are the cumulative percentage of organisms inhibited at the clioquinol concentrations indicated in the heading as micrograms per milliliter (μg/mL); and that all strains, without exception, were inhibited at concentrations below 100 μg/mL.

The comment further stated that the Panel incorrectly identified the growth medium used in the agar dilution MIC determination as Dermatophyte Sporulation Test agar (47 FR 12480 at 12497), when in fact the medium used was Diagnostic Sensitivity Test Agar (DST) (oxoid), the medium recommended by the World Health Organization for conducting sensitivity tests. The comment also disagreed with the Panel's determination that the MIC for *Pseudomonas aeruginosa* (*P. aeruginosa*) was greater than 128 μg/mL, when actually only 24 percent of the 165 strains of *P. aeruginosa* tested had an MIC greater than 128 μg/mL.

The agency has reviewed the analysis submitted by the comment and concurs with the comment's assessment as described above. Although the comment did not specifically request that an antibacterial claim be allowed, the agency considers it appropriate to note here that such a claim as it relates to antifungal activity remains in Category III as the Panel recommended (47 FR 12553).

**References**

(1) Ciba-Geigy Laboratories (U.S.A. and Switzerland), "Inhibitory Activity of Vioform," unpublished study in OTC Volume 070233.

(2) Scherrer, M., et al., "The Antimicrobial Activity of Broad-Spectrum Antimicrobials with Special Regard to Salicylic Acid," *Mykosen*, 14:323-334, 1971.

*E. Comment on Coal Tar*

10. One comment noted the Panel's Category II recommendation for coal tar as a topical antifungal ingredient and, while not taking issue with the recommendation, expressed concern that the decision may have been based on relative safety and effectiveness grounds. The comment stated that the Panel considered animal studies and anecdotal human studies, but did not include recent retrospective human studies. Therefore, the Panel did not provide a balanced review of the available information. The comment provided information on the chemistry and toxicity of medicinal coal tar and referred to the symposium on coal tar held by the Antimicrobial II and Miscellaneous External Panels on June 25, 1977 (Ref. 1). The comment pointed out that the composition of medicinal coal tar is more consistent than indicated in the Panel's report and that data presented at the symposium (but not cited in the Panel's report) and other data (Refs. 2, 3, and 4) indicate there is not a significant carcinogenic burden from the proper use of medicinal coal tar.

The Panel's review of coal tar as an antifungal was based on data available to it at the time that it met. The Panel noted that there were abundant data on the carcinogenic potential of coal tar and that there were no double-blind controlled clinical studies supporting the effectiveness of this ingredient as an antifungal (47 FR 12480 at 12516). In the tentative final monograph for OTC dandruff, seborrheic dermatitis, and psoriasis drug products, the agency discussed the results of more recent studies that evaluated the carcinogenic risks from using medicinal coal tar and proposed that coal tar be classified as Category I for use in control of all three conditions because the agency believes that, for these uses, the benefits to be derived from coal tar outweigh the potential risks. (See 51 FR 27346; July 30, 1986.)

Although the comment submitted additional information, it did not dispute the Category II classification of coal tar as an antifungal. Coal tar remains in Category II in this tentative final monograph because no new data have been submitted to show that it is effective for antifungal use.

**References**

(1) Summary Minutes of the 27th Meeting of the Advisory Review Panel on Antimicrobial (II) Drug Products, June 24–26, 1977.

(2) Pittelkow, M.R., et al., "Coal Tar, Ultraviolet Light and Cancer," *Journal of the American Academy of Dermatology*, 4:234–235, 1981.

(3) Maughan, W.Z., et al., "Incidence of Skin Cancers in Patients with Atopic Dermatitis Treated with Coal Tar," *Journal of the American Academy of Dermatology*, 3:612-615, 1980.

(4) Stern, R.S., et al., "Skin Carcinoma in Patients with Psoriasis Treated with Topical Tar and Artificial Ultraviolet Radiation," *Lancet*, 1:732–735, 1980.

*F. Comment on Menthol*

11. One comment requested that menthol be reclassified from Category II to Category III for effectiveness and from Category III to Category I for safety. The comment noted that the Panel had placed menthol in Category III in the information copy of its report (dated November 1979), stating that menthol was a "potentially viable antifungal ingredient" and that an in vitro study and one clinical study were required to establish proof of its effectiveness. However, in the advance notice of proposed rulemaking (47 FR 12480), the Panel placed menthol in Category II for effectiveness. The comment maintained that the Panel's original findings were consistent with a Category III classification for menthol and that the change to Category II was unwarranted.

The comment also disagreed with the Panel's conclusion that there are insufficient safety data for menthol in concentrations greater then 0.2 percent. The comment cited the conclusions of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products (Topical Analgesic Panel) that menthol is safe for topical analgesic, anesthetic, and antipruritic use in concentrations of 0.1 to 1 percent and as a counterirritant at 1.25 to 16 percent (44 FR 69768 at 69827; December 4, 1979).

The information copy of the Panel report was a preliminary report; the final decisions of the Panel were presented in its report published in the **Federal Register** on March 23, 1982 (47 FR 12480). In its final report, the Panel concluded that, although menthol may be useful in providing symptomatic relief of fungal infections through its antipruritic action, it is not an effective antifungal ingredient. Thus, the Panel classified menthol in Category II. The agency has reviewed the data evaluated by the Panel (47 FR 12517) and agrees with the Panel's conclusion that the limited in vitro data available show menthol to be a poor fungicide.

The agency agrees with the comment that menthol has been shown to be safe at concentrations greater than 0.2 percent. In the tentative final monograph for OTC topical analgesic drug products (48 FR 5852 at 5867; February 8, 1983), menthol was included as an analgesic, anesthetic, or antipruritic at concentrations of 0.1 to 1 percent and as a counterirritant at concentrations of 1.25 to 16 percent. However, counterirritants carry a warning against use on wounds or damaged skin; therefore, the concentrations approved for counterirritant use would not be appropriate for athlete's foot, jock itch, or ringworm. The agency considers menthol concentrations of 0.1 to 1 percent safe (Category I) for topical applications of athlete's foot, jock itch, or ringworm. Concentrations greater than 1 percent will remain as Category III for safety.

Because no new data have been submitted on the effectiveness of menthol as an antifungal agent, the agency is classifying this ingredient in Category II for efficacy in this proposed rule.

*G. Comments on Phenol*

12. Two comments disagreed with the Antimicrobial II Panel's Category II classification of phenol/phenolate sodium at less than or equal to 1.5 percent concentration for antifungal use (47 FR 12480 at 12519). Both comments pointed out that four other OTC advisory review panels placed phenol in Category I for safety: Dentifrice and Dental Care and Antimicrobial I Panels at concentrations up to 1.5 percent (47 FR 22712 at 22734 (May 25, 1982) and 39 FR 33102 at 33133 (September 13, 1974)), Oral Cavity Panel at concentrations of 0.5 to 1.5 percent (47 FR 22760 at 22814 (May 25, 1982)), and Topical Analgesic Panel at concentrations of 0.5 to 2 percent (44 FR 69768 at 69832).

One of the comments (Ref. 1) submitted copies of some of the studies (Refs. 2 through 12) submitted to the Antimicrobial II Panel and one new study (Ref. 13) on a phenol-based mouthwash. The comment also submitted animal safety data already reviewed by the Panel and requested Category I status for safety. The comment also contended that "the uncontrolled in vivo studies submitted to the Antimicrobial II Panel indicate that phenol/phenate [phenolate] sodium has been demonstrated to be more effective than other Category III ingredients."

The other comment (Ref. 14) asserted that the data are not consistent with Category II classification and requested that phenol/phenate [phenolate] sodium be placed in Category I for safety and Category III for effectiveness. The comment discussed several studies (Refs. 2 through 5) that were submitted to the Panel and claimed that these studies demonstrated no adverse effects of phenol/phenolate when applied to both broken and intact skin. The comment also discussed studies by a number of clinical investigators (Refs. 6 through 12) on the use of phenol/phenolate sodium on oral and vaginal mucosal membranes and stated that no irritant, toxic, or sensitizing effects were observed in any of the studies. The comment contended that these studies demonstrate the safety of phenol/phenolate sodium when used to treat athlete's foot and similar dermatologic disorders exhibiting broken and denuded epithelialized areas. Both comments stated that the Panel's conclusion "that the symptomatic and pruritic relief which would be offered by the inclusion of phenol/phenate [phenolate] sodium does not justify the potential risk of skin irritation or systemic toxicity that may result from the topical application of the formulation" was not consistent with in vivo and in vitro studies conducted, nor with the fact that millions of consumers have used the ingredients for more than 30 years with no reportable adverse effects.

The agency acknowledges that four other panels described by the comments have placed phenol/phenolate sodium in Category I for safety. Two of these panels, the Oral Cavity Panel and the Dentifrice and Dental Care Panel, evaluated the use of phenol on oral mucosa. The studies submitted by the comments on the safety of phenol on oral mucosa (Refs. 6 through 11 and 13) involved the short-term use of a combination product on the throat. The agency believes that, because the throat is constantly moist, use of the ingredient in this area is not considered analogous to the use of the ingredient on broken or intact skin infected with fungus. The comment also submitted an uncontrolled study (Ref. 12) which reported the safe use of a combination product containing sodium phenolate and phenol (less than 2 percent) on the vaginal mucous membranes of 529 gynecological patients with cervicitis or for prehysterectomy surgery or vaginitis. Three of the four studies (Refs. 3, 4, and 5) submitted by the comments in support of the safety of phenol on skin were uncontrolled clinical studies using a preparation containing sodium phenolate, phenol (less than 2 percent), menthol, thymol, sodium tetraborate, glycerin and either methyl salicylate or chlorophyll. The fourth skin study (Ref. 2) was a repeated insult patch test using an unspecified combination product. All of the studies lack details of material, methods, and evaluation procedures. Thus, the reported results (no toxic or sensitizing effects) in some of these studies are considered supportive information but are not adequate to demonstrate the safety of phenol at concentrations of 1.5 percent or less when applied to broken or intact skin infected with fungus.

The agency is concerned about the safe use of phenol/phenolate sodium in the treatment of athlete's foot, jock itch, and ringworm. In the tentative final monograph for OTC external analgesic drug products, the agency proposed that phenol/phenolate sodium carry the label warning "Do not apply over large areas of the body or bandage" and that use be limited to 7 days if symptoms persist (48 FR 5852 at 5868 to 5869). In considering phenol/phenolate sodium as an antifungal agent, the Antimicrobial II Panel was concerned that using phenol in athlete's foot, jock itch, and ringworm would be similar to using it under a bandage because the affected areas would be covered by clothing (47 FR 12480 at 12518). The Panel noted that "in most reports of toxicity from dilute solutions of phenol, bandaging the application was necessary to produce severe local changes." The Topical Analgesic Panel also recommended that preparations containing 1 to 2 percent phenol should be applied only to the smallest area needing treatment and should not be bandaged to prevent severe skin irritation (44 FR 69768 at 69833). Because it may be necessary to use an antifungal drug for 4 weeks to clear the infection, this prolonged exposure period and the occlusion of the affected area increase the potential risk of skin irritation and systemic toxicity from phenol. Data are needed to establish that phenol/phenolate sodium is safe for use under these conditions.

For these reasons, the agency agrees with the Panel that more data are needed to demonstrate that phenol/phenolate sodium in concentrations less than or equal to 1.5 percent is safe for use in the treatment of athlete's foot, jock itch, and ringworm. Therefore, phenol/phenolate at less than or equal to 1.5 percent is classified in this tentative final monograph as Category III for safety for use as an antifungal.

With regard to effectiveness, the Panel found that the in vitro concentrations required for effective antifungal action often exceed 1.5 percent concentration of phenol (47 FR 12480 at 12517). The studies (Refs. 3, 4, and 5) referred to by the comment to support the statement that phenol is more effective than other Category III ingredients were uncontrolled studies with a product containing less than 2 percent phenol and a number of other ingredients, as mentioned above. None of the studies met the Panel's guidelines for effectiveness testing of an active ingredient for fungicidal or fungistatic activity. The agency finds the results of the studies inadequate to demonstrate the efficacy of phenol as an antifungal drug and, therefore, is classifying phenol/phenolate in Category III for effectiveness.

**References**

(1) Comment No. C00011, Docket No. 80N-0476, Dockets Management Branch.

(2) Leach, E. D., An Unpublished Controlled Skin Sensitivity Study, Milligan College, TN, June 1970, in OTC Volume 070101.

(3) Freeman, C. W., " Evaluation of Chloraderm in the Topical Therapy of 'Athlete's Foot,' " *Medical Annals of the District of Columbia*, 32:98-99, 1963.

(4) Freeman, C. W., J. G. Gathings, and T. Gopinathan, "Evaluation of Chloraderm as a Dermatologic Agent," *Medical Annals of the District of Columbia*, 30:213-215, 1961.

(5) Streiker, F. B., "Chloraderm in Tinea Pedis," *Journal of the American Podiatry Association*, 54:29-30, 1961.

(6) Pinson, T. J., and J. Stanback, "Evaluation of Choloraseptic Solution as an Anesthetic Mouthwash," *The Quarterly of the National Dental Association*, 22:49-52, 1964.

(7) Blum, B., "Clinical Evaluation of an Anesthetic Mouthwash," *The New York State Dental Journal*, 26:419-421, 1960.

(8) Novick, J. M., and G. S. Sodhi, "Evaluation of Chloraseptic," *Medical Annals of the District of Columbia*, 29:427-430, 1960.

(9) Giles, J.W., and A.L. Bookhardt, "A Preliminary Report on the Use of Chloraseptic by the ENT Service," Veterans Administration Hospital, AL, unpublished paper, pp. 1-4, 1960, in OTC Volume 070101.

(10) Braunlin, E.A., "Evaluation of an Antiseptic Anesthetic Solution," *Journal of the National Medical Association*, 56: 151-152, 1964.

(11) Schwartz, T.A., and W.H. Slassman, "Evaluation of Chloraseptic, A New Topical Preparation for Relief of Sore Throat," galley proof in OTC Volume 070101.

(12) Smith, C.E., and J.F.J. Clark, "Gynaseptic in the Treatment of Vaginitis," *Journal of the National Medical Association*, 55:317-319, 1963.

(13) Breazeale, J., "Comparison of Cationic-Surfactant and Phenol-Based Mouthwash-Gargles in Relieving Oropharyngeal Pain," *Journal of the American College Health Association*, 23:165-166, 1974.

(14) Comment No. C00015, Docket No. 80N-0476, Dockets Management Branch.

*H. Comments on Povidone-iodine*

13. One comment submitted data (Ref. 1) addressing two of the Panel's concerns on povidone-iodine: The availability of elemental iodine from the complex and the stability of povidone-iodine (47 FR 12480 at 12546). The comment stated that substantial data were submitted to the OTC Antimicrobial (I) Panel and other panels showing that iodine is freely released from the complex, and the rate of iodine release is controlled by tissue demand. The comment contended that at equilibrium any iodine that is removed from the complex is replaced within less than 25 milliseconds (ms) (Refs. 2 and 3). The comment pointed out that chemical titration studies were submitted to the antimicrobial rulemaking, and these studies show that povidone-iodine provides the same amount of available iodine as tincture of iodine (Ref. 4). Regarding the stability of the complex, the comment contended that even if a stability issue existed it would be outside the scope of the review because stability is covered by the Current Good Manufacturing Practice regulations (CGMP) (21 CFR parts 210 and 211). The comment stated that, under the CGMP regulations, minimum standards have been set to ensure product stability for finished drug products (21 CFR 211.166), and the manufacturer of the finished dosage form is responsible for complying with these stability standards. The comment added that expiration dating as well as appropriate storage conditions are determined through required written testing programs.

The Panel considered povidone-iodine to be safe, but recommended that further studies were needed on the stability of povidone-iodine and on the availability of elemental iodine from the complex. The agency has reviewed the data submitted regarding availability (Refs. 2 and 3) and agrees with the comment that iodine is rapidly released from the povidone-iodine complex. According to Schenck et al. (Ref. 2), a povidone-iodine solution at a concentration of 1 to 10 percent contains over 99 percent complexed iodine. The concentration of free iodine in the solution reaches a maximum of $8 \times 10^{-5}$ moles/liter. At equilibrium, the povidone-iodine complex is self-monitoring. The rate of iodine release from the complex is controlled by tissue demand, and any iodine that is removed from the complex would be replaced within less than 25 ms (Ref. 3).

The agency also agrees with the comment that issues regarding stability would be governed by the CGMP regulations (21 CFR parts 210 and 211). These regulations require a written testing program to assess the stability of finished products and to determine appropriate storage conditions and an expiration date. Section 211.137(a) requires that drug products bear an expiration date supported by appropriate stability testing. However, § 211.137(g) provides that expiration dating requirements are not enforced for human OTC drug products if their labeling does not bear dosage limitations and they have been shown to be stable for at least 3 years by appropriate stability data. Therefore, FDA concludes that further submissions of data on the stability of povidone-iodine are not needed for purposes of this rulemaking proceeding. For additional information, see the agency's comments on the stability and availability of povidone-iodine in connection with the rulemaking for OTC topical acne drug products (Ref. 5). (See also the **Federal Register** of January 15, 1985; 50 FR 2172 at 2173.)

**References**

(1) Comment No. C00012, Docket No. 80N-0476, Dockets Management Branch.

(2) Schenck, H.U., et al., "Structure of Povidone-Iodine," *in* "Current Chemotherapy and Infectious Disease," Vol. I, American Society of Microbiology, Washington, pp. 477-478, 1980.

(3) Ditter, W., D. Horn, and E. Luedekke, "Thermodynamic and Kinetic Examinations Concerning the Complex Binding State and the Rate of Liberation of Iodine from Aqueous Iodine-PVP-Solutions," included in Comment No. C00012, Docket No. 80N-0476, Dockets Management Branch.

(4) Comment No. C00108, Docket No. 75N-0183, Dockets Management Branch.

(5) Letter from W. E. Gilbertson, FDA, to L. Blecher, GAF Corp., coded LET004, Docket No. 81N-0114, Dockets Management Branch.

14. One comment submitted the results of a clinical study (Ref. 1) in response to the Panel's statement (47 FR 12480 at 12546) that a double-blind, placebo-controlled clinical trial was needed to determine the effectiveness of povidone-iodine for the treatment of athlete's foot, jock itch, and ringworm.

The comment also included a statistical analysis of the study (Ref. 2) and the results of an in vitro assay of two povidone-iodine solutions for antifungal activity (Ref. 3). The comment stated that these data should be sufficient to meet the Panel's requirement for reclassifying povidone-iodine into Category I for effectiveness.

In the clinical study (Ref. 1), 40 patients with clinically and laboratory diagnosed athlete's foot were divided into two groups, one group using a 10-percent povidone-iodine solution and the other using the same solution without the povidone-iodine. Patients applied the medication to all involved areas of the feet every morning and night for 4 weeks. Cultures and potassium hydroxide (KOH) preparations were done before the study and repeated at the end of the treatment period and at a followup visit 4 weeks later. Signs and symptoms were scored weekly during treatment and at the followup visit. When the patients were evaluated at the end of the treatment period and signs and symptoms, KOH preparations, and cultures were considered simultaneously, the patients using povidone-iodine solution had a 68.4-percent therapeutic cure rate whereas the patients using placebo had a 30-percent therapeutic cure rate (Ref. 2). These cure rates were sustained to 4 weeks after therapy, and the difference is statistically significant ($p<0.05$). No side effects were reported in the study.

An in vitro study (Ref. 3) was performed to show that there was no difference in the fungicidal activity of the povidone-iodine solution used in this study, which also contained 0.05 percent methyl salicylate, and an identical solution of 10 percent povidone-iodine without the methyl salicylate.

The agency concludes that this study, along with the information previously reviewed by the Panel, provides adequate evidence of the safety and effectiveness of 10 percent povidone-iodine in the treatment of fungal infections such as athlete's foot, jock itch, and ringworm. Therefore, the agency is proposing that 10 percent povidone-iodine be classified Category I for this indication.

The agency's detailed comments and evaluations are on file in the Dockets Management Branch (Ref. 4).

**References**

(1) Jolly, H. W., "Final Clinical Summary: Double-Blind Comparison Study of Isodine Athlete's Foot Solution Versus Placebo in the Treatment of Patients with *Tinea Pedis*," unpublished study submitted with Comment No. C00005, Docket No. 80N-0476, Dockets Management Branch.

(2) Jolly, H. W., and R. G. Mora, "Final Statistical Report: Double-Blind Comparison Study of Isodine Athlete's Foot Solution Versus Placebo in the Treatment of patients with *Tinea Pedis*," unpublished study in Comment No. C00005, Docket No. 80N-0476, Dockets Management Branch.

(3) Axler, D., "Final Clinical Summary: *In vitro* Assay of Two Povidone-Iodine Solutions for Antifungal Activity," unpublished study in Comment No. C00005, Docket No. 80N-0476, Dockets Management Branch.

(4) Letter from W. E. Gilbertson, FDA, to E. A. Conrad, The Perdue Frederick Co., Coded LET012, Docket No. 80N-0476, Dockets Management Branch.

*I. Comment on Rubbing Alcohol*

15. One comment noted that rubbing alcohol applied between the toes morning and night is one of the most economical methods of controlling and eliminating athlete's foot as well as maintaining cleanliness of the feet. The comment suggested that the public be made aware of this economical alternative to more expensive OTC drugs that may not be as effective a remedy.

A number of alcohols were included in the products submitted to the Panel for review. The Panel considered these ingredients as possible antifungal agents based on the available literature and in some cases based on concentrations reported in a submission. The Panel concluded that these alcohols are inactive ingredients when used in products labeled for fungal infections of the foot, body, or groin (47 FR 12480 at 12485). Because the comment did not submit any data to support its contention that rubbing alcohol is an effective athlete's foot treatment and because the agency is not aware of any rubbing alcohol product labeled for antifungal use, the agency is unable to evaluate the basis for the comment's conclusion. Therefore, rubbing alcohol is not being classified in this rulemaking.

*J. Comment on Tannic Acid*

16. One comment requested that tannic acid be reclassified from Category II to Category III. The comment noted that the Panel had placed tannic acid in Category III in the information copy of its report (dated November 1979), stating that tannic acid was a "potentially viable antifungal ingredient" and that an in vitro study and one clinical study were required to establish proof of its effectiveness. No safety issues were raised. However, in the advance notice of proposed rulemaking (47 FR 12480), the Panel placed tannic acid in Category II. The comment maintained that the Panel's original placement of tannic acid in Category III was consistent with the criteria for other ingredients classified in Category III in the published report and that the change to Category II was unwarranted.

The information copy of the Panel report was a preliminary report; the final decisions of the Panel were presented in its report published in the **Federal Register** of March 23, 1982 (47 FR 12480). In its final report, the Panel reassessed the available data and concluded that the inclusion of tannic acid in antifungal medications is largely of historical interest. Having found no in vitro or clinical data on the effectiveness of tannic acid, the Panel concluded that this ingredient is not effective in the treatment of athlete's foot, jock itch, or ringworm and placed it in Category II (47 FR 12521). The agency has reviewed and agrees with the Panel's conclusions on tannic acid. Because no new data have been submitted, the agency is classifying tannic acid in Category II in this proposed rule.

*K. Comment on Thymol*

17. One comment requested that thymol be reclassified from Category II to Category III for effectiveness and from Category III to Category I for safety. The comment noted that the Panel had placed thymol in Category III in the information copy of its report (dated November 1979), stating that thymol was a "potentially viable antifungal ingredient" and that an in vitro study and one clinical study were required to establish proof of its effectiveness. However, in the advance notice of proposed rulemaking (47 FR 12480), the Panel placed thymol in Category II for effectiveness. The comment maintained that the Panel's original findings were consistent with a Category III classification for thymol and that the change to Category II was unwarranted.

The comment also disagreed with the Panel's conclusion that there are insufficient safety data for thymol in concentrations greater than 0.2 percent. The comment cited the conclusions of the Topical Analgesic Panel that "clinical use has confirmed that thymol is safe in the dosage range used as an OTC external analgesic" and that "thymol has little effect when applied topically to the skin and is virtually unabsorbed" (44 FR 69768 at 69855).

The information copy of the Panel report was a preliminary report; the final decisions of the Panel were presented in its report published in the **Federal Register** of March 23, 1982 (47 FR 12480). In its final report, the Panel

placed thymol at concentrations greater than 0.2 percent in Category II because the only clinical trial in which thymol was evaluated showed it to be ineffective in clearing athlete's foot and often irritating (47 FR 12523).

The agency has reviewed and agrees with the Panel's conclusions on thymol. The agency concludes that there are insufficient data to determine the safety of thymol at concentrations greater than 0.2 percent. The Panel determined and the agency concurs that additional data are needed to ensure the safety of thymol at concentrations greater than 0.2 percent. Based on the information it reviewed, the Panel concluded that more data are necessary on the absorption of thymol from small areas of application to broken and intact skin, on the local effects of thymol on wound healing, and on the irritation potential of thymol (47 FR 12522). However at concentrations less than or equal to 0.2 percent, thymol is safe and may be used as an inactive ingredient in formulations for product identification. The agency concurs with this recommendation.

The agency also notes that the Topical Analgesic Panel only reviewed thymol for use as an OTC external analgesic. That Panel referred thymol "to another Panel for the determination of its safety and efficacy as an antimicrobial and antifungal agent" (44 FR 69768 at 69855). Because of the different nature of the skin conditions being treated, the agency does not believe that the Topical Analgesic Panel's conclusions are applicable to the antifungal use of thymol.

Because no new data have been submitted on the effectiveness of thymol, the agency is classifying this ingredient in Category III (safety) and Category II (effectiveness) in this proposed rule.

*L. Comments on Tolnaftate*

18. Two comments stated that tolnaftate should be permitted to be labeled for the prevention of jock itch in addition to the prevention of athlete's foot. The comments noted that the Panel's reservation about long-term use of any antifungal agent in the groin (47 FR 12480 at 12490) was applied generally to all ingredients without regard to the safety margin of any ingredients. One comment added that the wide margin of safety of tolnaftate, including a very low potential for irritation, has been well established both through laboratory and clinical studies and through extensive use experience. The comment stated that results of this experience were presented to the Panel in oral and written submissions and by cross-reference to data contained in the new drug application for tolnaftate. The other comment asserted that after 19 years of extensive controlled and uncontrolled human studies, as well as lifetime studies in animals, tolnaftate is completely nontoxic to man and animal, and the potential for systemic absorption of tolnaftate through sensitive genital tissues and the groin with resultant toxicity is a nonexistent risk.

Although the safety of tolnaftate in the treatment of athlete's foot, jock itch, and ringworm is well established, the agency agrees with the Panel's recommendation that claims of prevention for this ingredient be limited to athlete's foot. The Panel concluded that tolnaftate may be used in the prevention of athlete's foot, but not in the prevention of jock itch or ringworm (47 FR 12480 at 12508). The Panel recognized that use of this ingredient for prevention of these fungal conditions would likely result in long-term use, whereas OTC treatment of a particular condition is limited to a specific time period. Because there is generally no limitation to the period of use when a product is used to prevent a condition, and because the groin is a more sensitive area than the feet, the Panel concluded that antifungal drugs, including tolnaftate, should not be used indefinitely in the groin (47 FR 12508). The comments did not submit any new data, but referred to studies that had been reviewed by the Panel. Those studies focused on the prevention of athlete's foot and not on jock itch. Therefore, the agency concludes that clinical studies on the prevention of jock itch are needed to establish the long-term safety of using tolnaftate or any other antifungal drug in the groin area. At this time, the agency finds insufficient data to support labeling tolnaftate for the prevention of jock itch. Although the comments did not discuss the prevention of ringworm, the agency considers it appropriate to express agreement with the Panel's statement that it would be impractical to use an antifungal agent prophylactically over large areas of the body to prevent ringworm (47 FR 12490 and 12508).

19. One comment contended that the Panel's Category I recommendation for a prophylaxis claim for tolnaftate was inconsistent with the Panel's own specific requirement of a study lasting a minimum of 12 weeks (47 FR 12480 at 12563). The comment argued that in one of the studies reviewed by the Panel three of the four centers participating in the study treated their patients for only 8 weeks (Ref. 1). The fourth center, which did test for 12 weeks, failed to show any difference between vehicle and tolnaftate therapy. The comment argued that two other studies reviewed by the Panel were also only conducted for 8 weeks (Refs. 2 and 3). The comment requested that the agency abandon the distinction between treatment and prophylaxis for antifungals because if an agent is effective in the treatment of a fungal infection it will also be effective in the prevention of the disease. As an alternate suggestion, the comment requested that the prophylaxis indication for tolnaftate be dropped. The comment also contended that the wording of § 333.250(b)(2) unfairly singles out tolnaftate. The comment requested that the heading for § 333.250(b)(2) should be in the same general format as § 333.250(b)(1), i.e., the word "tolnaftate" should not be in the heading for § 333.250(b)(2).

A reply comment stated that the referenced studies do, in fact, meet the criteria established by the Panel for prophylaxis and that the Panel properly applied these criteria in evaluating the clinical data on tolnaftate. The reply comment submitted a copy of an oral presentation made to the Panel which explains the results of the studies (Ref. 4).

The agency has reevaluated the data reviewed by the Panel to support its Category I recommendation for a prophylaxis claim for tolnaftate. The study by Charney et al. (Ref. 1) was conducted at four centers (California, Mississippi, Puerto Rico, and Texas), with a total of 168 subjects who entered the study with no evidence of fungal infection. At three of the four centers (California, Mississippi, and Puerto Rico), therapy was continued for 12 weeks with evaluations either taking place at 4, 8, and 12 weeks (Mississippi) or during the last 4 weeks of the 12-week period (California and Puerto Rico). At the other center (Texas), therapy was given for about 8 weeks. Thus, at three of the four centers the study met the Panel's 12-week criteria for length of the trial because therapy continued during the evaluation period.

The study showed that subjects treated with tolnaftate were significantly more likely to be free of athlete's foot at the end of the treatment period than were the control subjects. When the subjects at the center that continued therapy for only 8 weeks are excluded from the analysis, the following results are obtained: 38 of 41 subjects treated with tolnaftate were negative (93 percent) while 48 of 63 subjects treated with placebo were negative (76 percent). Regarding the comment's concern about the

significance of the results from one of the centers, the agency concludes that results with a p-value of less than 0.05 were obtained by pooling data from the three centers with 12-week trials.

In the study by Burrill and Nemlick (Ref. 2), therapy also continued for 12 weeks. The therapy consisted of an 8-week treatment period for each subject and a 4-week evaluation period, during which therapy continued. The study concluded that tolnaftate powder was superior to placebo in preventing the occurrence of athlete's foot in subjects free of tinea pedis at the start of the study. The study by Smith, Dickson, and Knox (Ref. 3) was similar in design to the Burrill and Nemlick study and arrived at a similar conclusion; however, the report of the Smith study did not make clear whether therapy continued during the evaluation period or only during the 8-week treatment period.

Although one part of the Charney study does not meet the Panel's 12-week criteria, the remainder of the Charney study and the Burrill and Nemlick study do meet the Panel's criteria, and the agency finds these studies adequate to support a prophylaxis claim for tolnaftate. Although the study by Smith, Dickson, and Knox does not meet the Panel's 12-week criteria, the results of the study can be considered supportive of the other two studies discussed above.

The agency disagrees with the comment's request to abandon a distinction between treatment and prophylaxis for antifungals. Treatment of an existing fungal condition and prevention of a condition are clearly different clinical entities. The intended use of the antifungal drug is different in each instance. Likewise, there is no reason to drop the prophylaxis indication for tolnaftate. This use has been satisfactorily established by the clinical data cited above.

However, the agency is revising the heading for § 333.250(b)(2), as suggested by the comment, so that it is consistent with the style and format of the other headings in the tentative final monograph.

**References**

(1) Charney, P., V. M. Torres, A. W. Mayo, and E. B. Smith, "Tolnaftate as a Prophylactic Agent for Tinea Pedis," *International Journal of Dermatology*, 12:179–185, 1973.

(2) Burrill, B. B., and A. S. Nemlick, "Prophylaxis of Tinea Pedis," *Journal of the Medical Society of New Jersey*, 67:629–631, 1970.

(3) Smith, E. B., J. E. Dickson, and J. M. Knox, "Tolnaftate Powder in Prophylaxis of Tinea Pedis," *Southern Medical Journal*, 67:776–778, 1974.

(4) Comment No. RC0002, Docket No. 80N–0476, Dockets Management Branch.

*M. Comments on Undecylenates*

20. One comment contended that under proper application of the governing scientific and legal standards FDA must conclude that the undecylenates are safe and effective for both treatment and prevention of athlete's foot, jock itch, and ringworm. The comment maintained that by definition an effective antifungal drug kills fungi and, with daily use, prevents the onset of infection. According to the comment, there is no evidence that fungi, unlike bacteria, develop resistance to topical agents, and separate prophylaxis studies are unnecessary to sustain prophylaxis claims. However, if separate evidence of prophylactic effect is to be required, the comment stated that such evidence has already been submitted to the agency for undecylenates (Ref. 1). In this study by Sulzberger and Kanof, 1,384 patients who received no treatment were compared with 1,213 patients treated with undecylenates. The researchers found that 28 percent of the untreated patients developed signs and symptoms of athlete's foot, but that only 4 percent of those on undecylenates developed the disease (Ref. 1). A reply comment reiterated the points made in the initial comment.

Another reply comment stated that the study of undecylenates by Sulzberger and Kanof (Ref. 1) falls quite short of the Panel's criteria to establish a prophylactic claim and gave the following reasons:

(1) No accurate record was made of actual treatment periods.

(2) No mycology was performed on any of the subjects. The only criterion was presence or absence of clinical symptoms.

(3) The control group received "no prophylactic agent" rather than a placebo vehicle control. This factor is especially important in a prophylactic study because the vehicle and proper hygiene make a significant contribution in the prevention of athlete's foot infections.

Another comment submitted new data consisting of the results of a study conducted with an undecylenate powder to prevent athlete's foot (Ref. 2). According to the comment, this study was designed in accordance with the Panel's recommendations, and the results of the study demonstrate the prophylactic effectiveness of undecylenates.

The Panel recognized that many Category I drugs effective in the treatment of athlete's foot might also be effective in its prevention. However, the Panel believed that data from human studies were necessary to support a prophylactic indication. The long-term effects of prophylactic drugs on the feet and on the fungi that cause athlete's foot are also not known. Accordingly, the agency concurs with the Panel that separate prophylaxis studies are necessary to support prophylactic claims.

With regard to the undecylenates, the agency concurs with the Panel and the reply comment that the study by Sulzberger and Kanof (Ref. 1), submitted to support a prevention claim for undecylenates, has the following serious deficiencies: The length of treatment was unclear; no potassium hydroxide (KOH) preparations or cultures were done; and the control group was "no treatment" controlled rather than "placebo vehicle" controlled.

The study submitted by the comment enrolled 87 subjects, some with and some without a history of athlete's foot; all had no lesions, negative cultures, and negative KOH preparations. Active drug (20 percent zinc undecylenate and 2 percent undecylenic acid) and vehicle were used in a double-blind manner. After 6 weeks of twice daily therapy, visual examination was performed on all patients and KOH preparations and cultures were done on those with lesions. Eight patients with positive mycological findings at week 6 were counted as prophylaxis failures and placed on therapy. All eight patients had been receiving the vehicle. Four other patients were dropped from the study for failing to appear at week 6. The remaining patients were kept on therapy until week 12, when cultures and KOH preparations were performed on all patients. No drug-related adverse effects were reported. The study, which included both 6-week and 12-week prophylaxis failures, concluded that infection occurred in 28 percent of the untreated groups, while infection occurred in only 7 percent of the treated group.

The agency has reviewed the study and finds that it does not provide sufficient evidence to support a claim for the effectiveness of undecylenates in the prevention of athlete's foot. A major flaw in this trial was the decision to perform mycological evaluations at week 6 only on those patients with visible foot lesions and to drop from the study those patients with positive mycology. Had mycological evaluations been done on all patients at week 6, additional failures (positive mycology but no clinical symptoms) might have been detected and the difference

between vehicle and treatment groups may not have been as large. This point takes on added significance when one considers that, at the end of the 12-week study, 3 of 31 patients in the vehicle control group had positive mycology while 3 of 38 patients in the treatment group were positive. In addition, double blinding may have been compromised by the elimination of eight patients from the placebo group. It is the agency's view that either all patients or no patients should have been cultured at week 6. Because the study included both patients with and without a previous history of athlete's foot, there would be an expected difference at 12 weeks between those 2 groups without treatment. There is no evidence that the groups were evenly balanced to rule out this factor. Further, the results of the study were incompletely reported with regard to the grading system for clinical signs and symptoms, and specific organisms cultured from each group. The apparently superior performance of the group treated with the undecylenates cannot be accepted as evidence for the prophylactic properties of the drug because of the deficiencies in the study design. A new properly-controlled study would be necessary to prove the prophylactic effect of the undecylenates.

The agency's detailed comments and evaluations are on file in the Dockets Management Branch (Ref. 3).

**References**

(1) Sulzberger, M. B., and A. Kanof, "Undecylenic and Propionic Acids in the Prevention and Treatment of Dermatophytosis," *Archives of Dermatology and Syphilology*, 55:391–395, 1947, included in OTC Volume 070306.

(2) Gundersen, K., "Use of Undecylenates in the Prophylaxis in Tinea Pedis," unpublished study in Comment No. LET008, Docket No. 80N–0476, Dockets Management Branch.

(3) Letter from W. E. Gilbertson, FDA, to R. E. Dann, Pennwalt Corp., Coded LET–13, Docket No. 80N–0476, Dockets Management Branch.

*N. Comments on Drug Combinations*

21. One comment disagreed with the Panel's 2.2-percent concentration limit for cresol in topical antifungal drug products. Citing the long marketing history of a particular product containing as its active ingredient a camphor metacresol complex (66-percent camphor and 22-percent metacresol), the comment stated that no adverse drug reactions have been reported and that the absence of complaints is especially significant considering that the product is primarily marketed to doctors, nurses, and paramedics. The comment cited a study submitted to the Panel to support the claim that there is strong evidence that a complex of camphor and metacresol exists and that only 1.5 percent of the metacresol in the product is "free" cresol (Ref. 1). The comment presented calculations showing that the daily exposure to metacresol from 80 milliliters (mL) of the product would be no more than 17 mL, released very gradually. According to the comment, this amount is many times lower than the lower toxic limit of cresol. The comment also referred to a National Institutes of Health (NIH) study on cresol that reportedly showed no toxic effect when the ingredient was injected subcutaneously in rabbits every second day for 2 weeks. The total amount injected was equivalent to 450 mL in a human adult (Ref. 2).

The comment indicated a willingness to limit the size of the container for its product to 1 fluid ounce and the recommended dose rate to 1 ounce applied in a 48-hour period in order to reduce further the amount of metacresol available for human exposure. The comment requested that, with these limitations on size and dose rate, the 66-percent camphor/22-percent metacresol combination be placed in Category I for safety and effectiveness.

The Antimicrobial II Panel proposed a concentration limit for cresol in topical antifungal drug products of 2.2 percent when combined with camphor in a 1-to-3 ratio. The Panel concluded that "evidence that a complex forms between metacresol and camphor [limiting the amount of the cresol to 1.5 percent] is lacking" and that "in the combination of 66 percent camphor and 22 percent metacresol all of the cresol would be available for absorption" (47 FR 12480 at 12536). To support its contention that only 1.5 percent of the metacresol in the product is free cresol, the comment cited only the study previously reviewed by the Panel (Ref. 1). The agency agrees with the Panel that this study does not provide adequate evidence of the amount of free cresol present. Without this evidence, the data on the toxicity of cresol in the NIH study (Ref. 2) are not directly applicable to the camphor/metacresol product.

Subsequently, in the rulemaking for OTC external analgesic drug products, the agency classified camphorated metacresol in a 3-to-1 ratio with a limit of 10.8-percent camphor and 3.6-percent metacresol as Category I for short-term use (i.e., 7 days) as an external analgesic (48 FR 5852 at 5858). The agency stated that there were insufficient data to establish general recognition of the safety of a concentration of metacresol greater than 3.6 percent when this ingredient is combined with camphor. The studies reviewed by the Topical Analgesic Panel and submitted to the agency in comments were very limited in scope. Most of the animal toxicity studies tested only one animal, observed the animal only for a short period of time, and did not include a detailed examination of the animal following drug application. Therefore, concentrations above 3.6-percent metacresol and 10.8-percent camphor were classifed in Category III. The use of camphorated metacresol as a first aid antiseptic will be addressed in the tentative final monograph for OTC first aid antiseptic drug products, to be published in a future issue of the **Federal Register.**

In regard to the comment's claim of "long history of safe use," marketing history alone cannot be regarded as adequate proof of safety. Moreover, there are no data showing that a limitation on the size of the container to 1 fluid ounce applied over a 48-hour time period would ensure safety. However, the agency believes, based on its previous determination in the external analgesic tentative final monograph and its pending determination in the first aid antiseptic tentative final monograph, that camphorated metacresol (a complex consisting of camphor and metacresol combined in a ratio of 3 parts camphor to 1 part metacresol) can be recognized as safe in OTC topical antifungal drug products. Concentrations above 3.6-percent cresol and 10.8-percent camphor remain in Category III for safety.

The effectiveness of metacresol as an antifungal agent has not been established. The Panel recommended one double-blinded clinical trial to determine the effectiveness of cresols in the treatment of athlete's foot, jock itch, and ringworm. The agency agrees with this recommendation. Until such a study is performed and evaluated and effectiveness is shown, camphorated metacresol at all concentrations remains in Category III for efficacy for antifungal use.

**References**

(1) Francis, A.W., "Physical Evidence of Association of Camphor with Phenol and the Cresols," *Journal of the American Pharmaceutical Association* (Scientific Ed.), 30:229–240, 1941, included on OTC Volume 070302.

(2) von Oettingen, W.F., "Phenol and Its Derivatives: The Relation Between Their Chemical Constitution and Their Effect on the Organism," *National Institutes of Health Bulletin*, No. 190, pp. 59–71 (1949), Public Health Service, The National Institutes of Health.

22. Two comments supported the Panel's recommendation to allow OTC combinations containing an antiperspirant and an antifungal ingredient. Referring to the agency's dissent in the preamble to the Panel's report in which FDA stated that it would not allow reformulation of these types of combination products to include Category I antifungal ingredients that are prescription to OTC "switches" (47 FR 12480 at 12481), the comments stated that whether or not the antifungals are "switch" ingredients has no relevance to whether or not the addition of an antiperspirant would enhance effectiveness or treat additional symptoms. The comments added that because there is no reason to believe that an antiperspirant could decrease the effectiveness of the antifungal and because the agency did not state any reservation about the safety of antiperspirants in antifungal combinations, combinations of antiperspirants and antifungals, including "switch" ingredients, should be placed in Category I. The comments contended that the rationale for such combinations, particularly for the treatment of athlete's foot, is threefold: (1) Moist conditions favor the growth of fungi; helping to keep the affected area dry should aid the antifungal drug in eliminating the fungi; (2) wetness, particularly in the toeweb area, is a common symptom of athlete's foot, and treating this symptom with an antiperspirant is consistent with the FDA combination policy; and (3) because bacterial growth is more likely to accompany fungal infection when the environment is moist, the addition of an antiperspirant should help keep the environment dry and thus minimize bacterial infection that may accompany athlete's foot.

A third comment noted the Panel's statement that moisture contributes to the development and continuation of athlete's foot and jock itch (47 FR 12480 at 12488) and requested that combinations containing an antifungal and an antiperspirant be classified in Category I both for the treatment of athlete's foot, jock itch, and ringworm and for the prevention of athlete's foot.

The Advisory Review Panel on OTC Antiperspirant Drug Products (Antiperspirant Panel) placed in Category I several active ingredients that had been shown through numerous clinical tests to be safe and effective antiperspirants when used in the axillae. (See the **Federal Register** of October 10, 1978; 43 FR 46694 at 46718 to 46719.) Although the Panel concluded that these ingredients would very likely reduce perspiration from other body surfaces, the Panel stated that to establish a standard for antiperspirant activity for the foot or hand, it is necessary to have information from the test subjects regarding their perception of effectiveness. The Panel did receive and evaluate two controlled studies (Ref. 1) that tested an aluminum chlorhydrate formulation as a foot antiperspirant. However, the Panel concluded that the data were not sufficient to support a claim of antiperspirant activity on body parts other than the axillae. Although the two controlled studies demonstrated a reduction of perspiration for the treated foot, the level of effectiveness was not correlated with user-perception of effectiveness. Therefore, in the absence of adequate user-perception effectiveness data, the Panel recommended that the claim of antiperspirancy on body surfaces other than the axillae be considered a Category III claim. In the tentative final monograph for OTC antiperspirant drug products, the agency concurred in the Panel's recommendation and placed claims for the use of antiperspirant drug products on the hands and feet in Category III (47 FR 36492 at 36497; August 20, 1982).

Although the agency did not directly state reservations about the safety of antiperspirants in antifungal combinations, it should be noted that the agency proposed that products covered by the tentative final monograph for OTC antiperspirant drug products contain the warning "Do not apply to broken skin" (47 FR 36504). Broken skin is common in fungal infections such as athlete's foot, jock itch, and ringworm. Data submitted to the Antiperspirant Panel suggested that the direct application of antiperspirant drug products to intact skin has not been associated with systemic toxic effects because of the relatively impermeable properties of the skin to metallic salts and complexes contained in antiperspirant drug products. In addition, results of percutaneous dermal toxicity tests performed on animals indicated no ill effects on the animals. However, some users of antiperspirant drug products have experienced local cutaneous irritation. Thus, although the Panel acknowledged that these adverse reactions are ordinarily not serious and are reversible, it recommended that antiperspirant drug products not be applied to open, broken, or abraded skin where the skin's barrier is breached (43 FR 46694 at 46707 to 46708).

The agency believes there is merit on one comment's argument that, because moisture contributes to the development and continuation of athlete's foot and jock itch, the combination of an antiperspirant to reduce moisture with an antifungal constitutes rational therapy. However, because broken skin is common in these infections and because sufficient data have not been submitted to demonstrate the safety of antiperspirants used on broken skin or to demonstrate effectiveness of antiperspirants used on the feet, groin, or other body parts except the axillae, the combination of an antifungal and an antiperspirant for the treatment of athlete's foot, jock itch, and ringworm and for the prevention of athlete's foot remains in Category III in this tentative final monograph.

There is a related issue concerning antifungal ingredients in combination with deodorant (cosmetic) ingredients. In the tentative final monograph for OTC antiperspirant drug products, the agency stated that deodorancy is a cosmetic claim and that the deodorant effectiveness of antiperspirant ingredients would not be further considered in that rulemaking (47 FR 36492 at 36494). Final OTC drug monographs do not address drug-cosmetic combination products, but cover only the drug aspects of products. If a product containing a monograph ingredient(s) is intended for both drug and cosmetic use, it must conform to the requirements of the final OTC drug monograph. In addition to the monograph labeling for OTC antifungal drug products, an antifungal-deodorant product must also bear appropriate labeling for cosmetic deodorant uses, in conformity with section 602 of the act (21 U.S.C. 362) and the provisions of 21 CFR part 701.

In accordance with the revised labeling requirements for OTC drug products, it is the agency's view that cosmetic claims may not appear within the boxed area designated "APPROVED USES." As discussed in the **Federal Register** of May 1, 1986 (51 FR 16258 at 16264 (paragraph 14)), cosmetic terminology is not reviewed and approved by FDA in the OTC drug monographs and therefore could not be placed in the box. Cosmetic claims may appear elsewhere in the labeling but not in the box, should manufacturers choose the labeling alternative provided in § 330.1(c)(2) (i) or (iii) for labeling cosmetic/drug products. Although the agency does not prohibit commingled drug and cosmetic labeling separate from the indications section, the agency requests that such claims be appropriately described so that consumers will more readily be able to differentiate the drug aspects from the

cosmetic aspects of such labeling. If commingled drug and cosmetic labeling claims are confusing or misleading, the agency may determine that the product's labeling is misleading within the meaning of the act and declare the product misbranded under sections 502(a) and 602(a) of the act (21 U.S.C. 352(a) and 362(a)).

The use of prescription to OTC "switch" antifungal ingredients in reformulated products is addressed in comment 24 below.

**Reference**

(1) OTC Volume 140017.

23. Three comments supported the Panel's recommendation that combinations of up to three Category I antifungal ingredients with hydrocortisone or hydrocortisone acetate (0.5 to 1 percent) should be available for OTC use in the treatment of athlete's foot, jock itch, and ringworm (47 FR 12480 at 12554). The comments listed the following reasons why such combinations are rational: (1) They are consistent with FDA's September 1978 combination policy guidelines, which provide that Category I active ingredients from different therapeutic categories may be combined to treat different symptoms concurrently (Ref. 1); (2) the less-than-effective classification by FDA of two prescription products (discussed in the preamble to the Panel's report at 47 FR 12481) appears to have been based solely on the lack of demonstrated contribution of hydrocortisone to the antifungal effectiveness of the products, rather than on a judgment concerning the ability of hydrocortisone to relieve the concurrent symptoms of burning and itching, which is the only reason that it is included in the combination product; (3) although the Topical Analgesic Panel recommended that hydrocortisone and hydrocortisone acetate be approved for OTC use only as single ingredients, it gave no reason for that position. If the Panel had simply wanted to exercise caution until widespread experience had been gained with OTC hydrocortisone products, such experience has now been accumulated with no safety problems apparent; and (4) consumers should have available a product that treats the fungal infection as well as relieves the burning and itching caused by the fungal infection.

Another comment agreed with and supported the Panel's conclusion that the specific combination of clioquinol and hydrocortisone is safe and effective for OTC use in the treatment of athlete's foot, jock itch, and ringworm. The comment recognized that FDA had previously declared this combination product as lacking substantial evidence of effectiveness within the meaning of the agency's combination drug product policy. (See the **Federal Register** of September 25, 1981; 46 FR 47408.) The comment stated its belief that the agency's position on the effectiveness of this combination product was erroneous and contradicted by the adequate and well-controlled clinical studies reviewed by the Antimicrobial (II) Panel and previously reviewed by the agency itself during its Drug Efficacy Study Implementation (DESI) deliberations. The comment included a copy of its November 24, 1981, submission to the DESI proceeding to support the Panel's conclusion that the combination of clioquinol and hydrocortisone is effective.

The comment added that the Panel's proposed labeling for the combination should be modified to distinguish it from the indications for use of clioquinol alone. The comment recommended that the following language be adopted for the indications for use of clioquinol/hydrocortisone products: "Iodochlorhydroxyquin [Clioquinol]/hydrocortisone is effective in the treatment (or cure) of athlete's foot, jock itch, and ringworm and is recommended when additional relief from associated redness, scaling, and itching is desired." The comment cited four studies (Refs. 2 through 5) to support its position that the combination provided significant improvement over clioquinol alone for scaling and itching and for healing of lesions.

As an initial matter, the agency acknowledges that the Panel mentioned that several combinations of an antifungal agent with hydrocortisone or hydrocortisone acetate 0.5 to 1 percent were submitted for evaluation, and that antifungal agents included in the various submitted combinations include clioquinol, miconazole nitrate, and calcium undecylenate. (See 47 FR 12480 at 12554.) As the Panel pointed out, double-blind controlled studies were not performed on combinations containing calcium undecylenate. The Panel also discussed some studies done with a 2-percent miconazole nitrate/1-percent hydrocortisone combination in Belgium and Colombia, South America. However, such a product has never been marketed in the United States, and, although supportive, these studies alone cannot be used to establish the general recognition of the safety and effectiveness of antifungal/hydrocortisone combinations for OTC use.

The agency has been evaluating the effectiveness of the clioquinol/hydrocortisone combination product under the DESI program. The agency's position is that there is a lack of substantial evidence that the combination product is effective for its labeled indications, and that the available data do not demonstrate that each component of the combination makes a significant contribution to the claimed effects of the drug. In the **Federal Register** of August 21, 1984 (49 FR 33173), the agency announced a formal evidentiary hearing on its proposal to withdraw approval of the prescription combination product composed of clioquinol/hydrocortisone because there are no adequate and well-controlled investigations (including clinical investigations) by experts qualified by scientific training and experience to evaluate the effectiveness of the drug to demonstrate that clioquinol/hydrocortisone is an effective combination and will have the effects claimed or suggested in its labeling. The hearing concluded in March 1986. On February 5, 1988, the FDA Administrative Law Judge issued an Initial Decision, concluding that there is a lack of substantial evidence of the effectiveness of the combination product, and ordering the new drug application (NDA) for the product withdrawn (Ref. 6). Exceptions to the Initial Decision and replies to the exceptions (Ref. 7) have been filed with the Dockets Management Branch and are currently under review by the Commissioner.

Because the agency believes that resolution of the status of the clioquinol/hydrocortisone combination in the DESI proceeding will be pivotal to the final classification of antifungal/hydrocortisone combinations in this rulemaking, the agency is deferring classification of such combinations in this rulemaking until all administrative remedies have been exhausted and the matter is fully resolved in the DESI proceeding.

The agency also notes that the data upon which the Panel based its recommendation were for combinations of single antifungal ingredients and hydrocortisone or hydrocortisone acetate. No data have been submitted to demonstrate the safety and effectiveness of a combination of up to three antifungal ingredients and hydrocortisone or hydrocortisone acetate. The agency has evaluated the Panel's recommendation that up to three antifungal ingredients may be combined and has found no evidence to establish that such a combination offers any

advantage over the antifungal ingredients when used alone and has placed this combination in Category III. (See comment 24 below.) The agency further notes that the Topical Analgesic Panel recommended that hydrocortisone and hydrocortisone acetate 0.25 to 0.5 percent be allowed OTC as single ingredients, but not in any combination. In the tentative final monograph for OTC external analgesic drug products, the agency concurred with the Panel's recommendation (48 FR 5852 at 5854). Also, as noted above, the studies on the miconazole nitrate/hydrocortisone combination product involved the use of hydrocortisone at a 1-percent concentration, a strength currently not approved for OTC marketing.

In conclusion, the combination of up to three Category I antifungal ingredients and hydrocortisone or hydrocortisone acetate is not being included in the tentative final monograph for OTC antifungal drug products at this time. The degree to which this combination complies with FDA's September 1978 combination policy guidelines is discussed further in comment 27 below, in which the combination of an antifungal with any Category I analgesic/anesthetic/antipruritic is addressed.

References

(1) Food and Drug Administration, "General Guidelines for OTC Drug Combination Products," September 1978, Docket No. 78D–0322, Dockets Management Branch.

(2) Brecker, L. J., et al., "Protocol #02," unpublished study in OTC Volume 070193.

(3) Abdel-Aal, H., et al., "A Double-Blind Comparison of a New Combination (Halcinonide-Neomycin-Amphotericin) and Active Controls in Cutaneous Candidiasis and Steroid-Responsive Dermatoses," *The Journal of International Medical Research*, 4:232–236, 1976.

(4) Barba-Rubio, J., "Clinical Evaluation of a New Halcinonide-Antifungal Combination," *Current Therapeutic Research*, 20:655–660, 1976.

(5) Carpenter, C. L., et al., "Combined Steroid-Antinfective Topical Therapy in Common Dermatoses: A Double-Blind, Multi-Center Study of Iodochlorhydroxyquin-Hydrocortisone in 277 Patients," *Current Therapeutic Research*, 15:650–659, 1973.

(6) Food and Drug Administration Initial Decision: "Proposal to withdraw Approval of the New Drug Application for Vioform-Hydrocortisone Cream, Ointment and Lotion Containing Iodochlorhydroxyquin and Hydrocortisone Under the Drug Efficacy Study Implementation Program, February 5, 1988, Coded IDF, Docket No. 80N–0012, Dockets Management Branch.

(7) Comments No. EXC00001, EXC00002, EXC00003, EXC00004, REX00001, and REX00002, Docket No. 80N–0012, Dockets Management Branch.

24. Two comments disagreed with the agency's decision not to allow the reformulation of combination products to include Category I ingredients where prescription to OTC switches are involved. The comments asserted that nowhere in the **Federal Register** of May 11, 1972 (37 FR 9464), which established the OTC drug review procedures, nor in the September 1978 guidelines for OTC drug combination products (Ref. 1), did the agency state that general recognition of the safety and effectiveness of ingredients for OTC use would be limited to those ingredients already marketed on an OTC basis. One comment also disagreed with the agency's decision to refuse to permit combinations of Category I antifungal ingredients and stated that the Panel's recommendation that a Category I combination may contain up to three antifungal ingredients "provided that each ingredient broadens the antifungal spectrum" (47 FR 12480) fully meets the FDA's combination policy (21 CFR 330.10(a)(iv)). The other comment pointed out that there is no precedent set by other panels for limiting switch ingredients to single-ingredient products except in the case of hydrocortisone, where the Topical Analgesic Panel recommended "a specific ingredient for a specific use." The comment added that the Antimicrobial II Panel intended its combination policy to encompass ingredients recommended for prescription to OTC switch. The comment urged that the Panel's recommendations be followed because the agency gave no rationale or justification for its restriction. The comment concluded that, in the absence of any stated rationale, the agency's decision is both arbitary and contrary to the purpose of the OTC drug review.

In the preamble to the Panel's report, the agency noted that the Panel had recommended that up to three Category I antifungal ingredients may be combined, provided that each ingredient broadens the antifungal spectrum, for the treatment of athlete's foot, jock itch, and ringworm. Under § 330.13 (12 CFR 330.13), combination products containing prescription-to-OTC switch antifungal drugs recommended as Category I by the Panel could have been marketed immediately following publication of the Panel's report and proposed monograph unless the agency disagreed with the Panel's recommendations at that time. FDA stated that it was not aware of any such Category I antifungal combinations on the OTC market at that time (47 FR 12480). The agency also stated that the Panel's report had been prepared independently of FDA, and that the agency had not yet fully evaluated the report. Therefore, the agency did not want new combination antifungal products containing switch drugs entering the OTC marketplace until it had fully evaluated the data relating to these products. The agency was willing, however, to permit reformulation of combinations of antifungal ingredients already on the OTC market to include Category I ingredients already in the OTC marketplace.

The agency has evaluated the Panel's recommendations that a combination may contain up to three antifungal ingredients provided each ingredient broadens the antifungal spectrum (47 FR 12480 at 12554). The agency has examined the antifungal spectra of the various Category I ingredients and determined that, with the exception of nystatin, the spectra of the various ingredients are similar. The ingredients clioquinol, tolnaftate, and undecylenic acid and its salts are effective against the dermatophytes cited by the Panel, namely, *T. rubrum*, *T. metagrophytes*, *E. floccosum*, and *M. canis*, in its criteria for evaluating the effectiveness of antifungal ingredients (47 FR 12491). In addition, the switch ingredients haloprogin and miconazole nitrate and effective against these four dermatophytes and *Candida*. Furthermore, the spectra of the switch ingredients are sufficiently broad as to make it unnecessary to combine these ingredients with any other Category I antifungal ingredient. Because of the similarity of spectra of the Category I antidermatophytic antifungal ingredients, combinations of up to three of these ingredients that are effective against the same dermatophytic fungi that cause athlete's foot, jock itch, and ringworm would not broaden the antifungal spectra. Clinical data are needed to show that a combination of any two of these ingredients would increase the spectrum of the product, or offer some other advantage over the single ingredients in terms of enhanced effectiveness, safety, patient acceptance, or quality of formulation, as provided in the OTC combination guidelines (Ref. 1). Also, the agency is not aware of any such combinations currently available on the market. Therefore, in the absence of data to support such combinations, the agency is not including combinations of antifungal ingredients effective against dermatophytic fungi in this tentatives final monograph.

Regarding the comment's reference to the guidelines for OTC drug combination products (Ref. 1), paragraph 3 of those guidelines states that Category I active ingredients from the same therapeutic

category that have the same mechanism of action may be combined in selected instances. However, the guidelines also state that such combinations must meet the OTC combination policy in all respects, offer some advantage over the active ingredients used alone, and, on a benefit-risk basis, be equal to or better than each of the active ingredients used alone at its therapeutic dose. The advantage of combinations of antifungals as defined by the Panel is the broadening of the antifungal spectrum. However, the spectrum was defined by the Panel as being those organisms that are the most common causes of jock itch, ringworm, and athlete's foot in the United States. Given this specific spectrum, combinations of Category I antifungal ingredients would not result in a broadening of the antifungal spectrum. No advantage over the active ingredients used alone has been shown to justify such combinations.

The Panel also stated that some fungal diseases are caused both by dermatophytes and by *Candida* and that, because most consumers cannot distinguish between these diseases, a combination containing an antidermatophytic ingredient, as discussed above, and an anticandidal ingredient, e.g., nystatin, would offer broader therapy (47 FR 12480 at 12554). However, the Panel did not cite any data to support this theory. In the absence of information showing that infection by *Candida* is a significant cause of athlete's foot or jock itch (see the Panel's discussion at 47 FR 12487), or that secondary infections of *Candida* are common, the combination of an antidermatophytic ingredient with an anticandidal ingredient is classified in Category III at this time. If information is submitted to the agency demonstrating that *Candida* is a significant problem in dermatophytic infections, the agency will consider data in support of the appropriations of these combinations. Specifically, these data would have to show increased effectiveness of the product resulting from the inclusion of nystatin in the combination product. As stated in the proposed rule for OTC antimicrobial drug products (43 FR 1210 at 1239; January 6 ,1978), "The Commissioner believes that antimicrobial agents are somewhat different from combinations of other OTC ingredients in that they act upon a foreign entity, the microorganism, rather than the host. In combinations of nonantimicrobial ingredients, the advantage of the combination may be that therapeutic activity is obtained at lower dosages for each component ingredient, whereas there can be no contribution of effectiveness of an antimicrobial ingredient by combining it with antimicrobial ingredients having identical bactericidal, virocidal, and fungicidal properties. Consequently, the Commissioner concludes that a rational combination of antimicrobials should have one of the following purposes: expansion of the microbial spectrum relevant to the product class for which the combination is intended, reduction of the toxicity of one or both of the ingredients, or a synergistic effect." This conclusion is equally applicable to antifungal drugs.

In conclusion, the agency is proposing in this tentative final monograph that all combinations of antifungal active ingredients, as permitted by the Panel in § 333.220(a), be placed in Category III. Because nystatin was included in the Panel's recommended monograph only for use in combination antifungal products, the agency is also placing nystatin in Category III because no combinations are currently included in the tentative final monograph.

**Reference**

(1) Food and Drug Administration, "General Guidelines for OTC Drug Combination Products," September 1978, Docket No. 78D–0322, Dockets Management Branch.

25. Two comments supported the Panel's recommendation at 47 FR 12480 at 12557 that an antifungal ingredient may be combined with a broad-spectrum antibacterial ingredient that is active against gram-positive and gram-negative bacteria for the treatment of athlete's foot. Although the Panel recognized the combination as rational, one of the comments questioned why the Panel required a double-blind, controlled clinical study to demonstrate the effectiveness of the combination. The comment stated that such a study was submitted to the Panel and was, in fact, the basis for the Panel's recognition of the need for an antifungal/antibacterial combination (Ref. 1). This comment asserted that the study was carefully conducted and that it adequately demonstrated the effectiveness of such therapy. Therefore, according to the comment, the only requirement for marketing such a combination should be the identification of appropriate Category I antibacterial agents and adding the combination of an antifungal and an antibacterial ingredient to the list of combinations in § 333.220 of the tentative final monograph.

The agency agrees with the Panel that a broad-spectrum antibacterial ingredient that is active against gram-positive and gram-negative bacteria is rational for use in combination with an antifungal for the treatment of athlete's foot. However, recognition of medical rationale by itself does not determine that this combination is generally recognized as safe and effective for the intended use. In fact, based on the data, including the study referred to by the comment, the Panel classified the combination in Category III (47 FR 12480 at 12557).

The study (Ref. 1), according to the authors, demonstrated that topical antibacterials produced definite clinical benefit in the treatment of athlete's foot, although the disease was "not cured, merely curbed," and that a combination of neomycin 1 percent and tolnaftate 1 percent was thought to be more effective than either treatment alone (47 FR 12557). After reviewing the study, the agency concurs in the Panel's conclusion that the combination of an antifungal with a broad-spectrum antibacterial is sometimes desirable for the treatment of athlete's foot characterized by soggy toewebs, but that a double-blind clinically controlled study is needed to show effectiveness (47 FR 12558). In addition, it should be noted that the Panel was concerned that chronic use of certain antibacterial ingredients could result in potential toxicity, including contact sensitization (47 FR 12558). Accordingly, the agency also concurs with the Panel that any antibacterial ingredient considered for inclusion in a combination antifungal product should be both safe and effective.

Because no new data on specific antibacterial/antifungal combinations have been submitted, such combinations remain in Category III in this tentative final monograph.

**Reference**

(1) Leyden, J. J., and A. M. Kligman, "Interdigital Athlete's Foot. The Interaction of Dermatophytes and Resident Bacteria," *Archives of Dermatology*, 114:1466–1472, 1978, in OTC Volume 070304.

26. One comment supported the Panel's recommended Category I combination of a keratolytic agent, e.g., salicylic acid, with up to three antifungal ingredients based on the action of an effective keratolytic that removes the outer layers of the stratum corneum, thus better exposing the infecting fungus to the action of the antifungal ingredients (47 FR 12480 at 12554). The comment disagreed with the agency's concerns about the lack of data to support such combinations and the concerns expressed by the Miscellaneous External Panel about the

safety of salicylic acid used on skin areas other than those being treated (47 FR 12481). The comment argued that antifungals are for use on areas directly affected and thus the antifungal/keratolytic combination should be allowed as Category I.

The agency notes that the Antimicrobial II Panel stated that, theoretically, an effective keratolytic agent such as salicylic acid could remove the outer layers of the stratum corneum, thus better exposing the infecting fungus to the action of the antifungal ingredient (47 FR 12554). In the preamble to the Panel's report, the agency noted that the Panel provided no data to support its recommendation and that there was no evidence submitted to the Panel to show that a keratolytic agent would be useful or safe in treating fungus conditions. The comment did not submit any safety and effectiveness data to support the use of keratolytics in general, or the use of salicylic acid in particular, in combination with antifungal ingredients. Although the combination may theoretically be useful, this alone is not an adequate basis to include such a combination in the tentative final monograph.

The Miscellaneous External Panel recommended that salicylic acid be classified as Category I as a corn and callus remover at concentrations from 12 to 40 percent in pads, plasters, and disks and at concentrations from 12 to 17.6 percent in collodion. (See the **Federal Register** of January 5, 1982; 47 FR 522 at 527.) The agency concurred with this recommendation in the tentative final monograph for OTC corn and callus remover drug products. (See the **Federal Register** of February 20, 1987; 52 FR 5412.)

The Miscellaneous External Panel also recommended that salicylic acid be classified as Category I as a wart remover at concentrations of 5 to 17 percent in a collodion vehicle. (See the **Federal Register** of October 3, 1980; 45 FR 65609 at 65613.) The agency concurred with this recommendation in the tentative final monograph for OTC wart remover drug products. (See the **Federal Register** of September 3, 1982; 47 FR 39102.) The agency further expanded the proposed monograph to include 12 to 40 percent salicylic acid in a plaster vehicle and redesignated "a collodion vehicle" as a "collodion-like" vehicle for the dosage form containing 5 to 17 percent salicylic acid. (See the **Federal Register** of March 27, 1987; 52 FR 9992.)

In discussing the safety of salicylic acid as an antifungal agent, the Antimicrobial II Panel stated that this drug was safe when used in a concentration less than or equal to 3 percent and if the use of the drug is restricted to relatively small body areas (47 FR 12480 at 12549). The Panel also pointed out that the systemic toxicity of topical salicylic acid, like its keratolytic effects, appears to result from a combination of factors. Some of these factors are (1) a high concentration of salicylic acid in a vehicle that allows rapid absorption, (2) the frequency of application, (3) whether the surface area is occluded, and (4) the condition and area of skin to which the preparation is applied (47 FR 12549).

Subsequent to these reports, the agency classified salicylic acid as Category I for use in acne drug products, but proposed to limit the concentration to a range of 0.5 to 2 percent because there may be an increased potential for irritation from concentrations greater than 2 percent. (See the **Federal Register** of January 15, 1985; 50 FR 2172). Broken, denuded, diseased, or infected skin areas occur in fungal infections. In the case of athlete's foot and jock itch (and often ringworm), the affected area is occluded after the drug product is applied. The agency is concerned that a keratolytic agent such as salicylic acid combined with antifungal ingredients may further irritate the skin, especially in areas likely to be occluded, particularly sensitive areas like the groin. The agency is also concerned about a possible occurrence of some systemic toxicity. Further safety data are needed to ensure that these problems will not occur with such a combination product.

With regard to efficacy, the effective keratolytic concentrations recommended by the Miscellaneous External Panel discussed above are higher than the "safe" 3 percent concentration recommended by the Antimicrobial II Panel and the "safe" 0.5 to 2 percent range proposed by the agency for topical acne drug products. If a lower concentration of the keratolytic agent must be used, it must also be shown that that concentration is effective. Also, as a combination drug product, evidence is needed to show that the keratolytic component contributes to the effect of the product. There is a lack of data showing that the antifungal-keratolytic combination is more effective than the antifungal agent used alone. Therefore, the agency classifies the combination of an antifungal(s) and a keratolytic agent for the treatment of athlete's foot, jock itch, and ringworm and for the prevention of athlete's foot as Category III for both safety and effectiveness.

27. Two comments disagreed with the Panel's Category II classification of an antifungal ingredient with a local anesthetic (47 FR 12480 at 12555). The comments contended that it is rational therapy and beneficial to the consumer to combine a Category I antifungal with any Category I analgesic/anesthetic/antipruritic ingredient identified in § 348.10(b) of the OTC Topical Analgesic Panel's recommended monograph for OTC external analgesic drug products (44 FR 69768 at 69865). One comment stated that curing the disease (i.e., athlete's foot, jock itch, and ringworm) ultimately results in relief of the symptoms of burning and itching, but that it often requires several weeks of treatment to accomplish with an antifungal drug alone. Therefore, the comments maintained that topical analgesics/anesthetics/antipruritics would provide prompt short-term relief of such common symptoms as itching while the antifungal agent treated the underlying disease.

Both comments mentioned that the Panel concurred with the basic rationale for these combinations (47 FR 12554), but that the Panel had expressed some concern regarding these combinations. According to the comments, the Panel's concern that use of an anesthetic/antifungal combination would result in the anesthetic's masking the symptoms without eradicating the fungus was addressed at 47 FR 12564 where the Panel specified that any product labeled as an antifungal must contain a Category I antifungal ingredient. Masking symptoms would not be a concern because the antifungal ingredient would be eradicating the fungus simultaneously. Another concern was that some individuals would stop treatment once symptomatic relief (of the itching) was obtained but before the infection was cured. The comments believed that this concern could be handled by including on the label the directions recommended by the Panel in § 333.250(d)(1), which state that best results in athlete's foot and ringworm are usually obtained with 4 weeks' use of the product and in jock itch, with 2 weeks' use. The comments asserted that this combination meets the general OTC combination drug requirement that provides that one basis for combining active ingredients is for the concurrent treatment of multiple symptoms. The comments did not submit any data.

The agency agrees with the comments that the combination of an analgesic/anesthetic/antipruritic with a Category I antifungal is rational and is consistent with the agency's OTC combination policy requirement that active ingredients may be combined if they provide concurrent treatment of multiple symptoms (Ref. 1). The agency also

agrees with the comments that the Panel's concerns could be addressed by ecific labeling in the monograph. wever, the recognition of medical ionale alone cannot establish that this combination is generally recognized as safe and effective for the intended OTC use. The purpose of combining the two individual components in this particular combination is to increase the effectiveness of the product in relieving burning and itching. Because the analgesic/anesthetic/antipruritic drug is being included in the combination to provide relief of burning and/or itching, an action that also results once the antifungal drug begins to cure the underlying disease, the contribution of the analgesic/anesthetic/antipruritic must be shown by demonstrating that the combination is more effective in relieving the burning and itching sooner (or in reducing the severity) than the antifungal drug used individually. The Panel found the data submitted to it to establish general recognition of the safety and effectiveness of such a combination to be inadequate, and the comments did not submit any additional data. However, based on the medical rationale presented by the comments, the agency is classifying these combinations in Category III, pending receipt of data on specific combinations. e also comment 23 above, which usses the combination of drocortisone with an antifungal.)

Reference

(1) Food and Drug Administration, "General Guidelines for OTC Drug Combination Products," September 1978, Docket No. 78N-0322, Dockets Management Branch.

28. One comment disagreed with § 333.250(b)(2) of the Panel's recommended monograph in which a claim for prevention of athlete's foot is limited to products containing tolnaftate "as a single ingredient." The comment argued that there is no reason to exclude a prophylaxis claim for combination products containing two Category I antifungal ingredients, where one or both are approved for prophylaxis, or for combination products containing an antifungal for prophylaxis and an antiperspirant. The comment requested that the heading for § 333.250(b)(2) be reworded as follows: "For products containing any ingredient identified in § 333.210(e) alone or in a combination identified in § 333.220(b)(1) labeled for the prevention of athlete's foot."

Claims for prevention of athlete's foot individual active ingredients are ussed in comments 18, 19 and 20 e. The agency has not received any ata showing that a combination antifungal drug products is safe and effective in the prevention of athlete's foot. Data would have to be submitted to demonstrate the contribution of each active ingredient in the product in preventing athlete's foot. Such combinations are classified in Category III in this tentative final monograph. Therefore, the heading of § 333.250(b)(2) is not being changed as requested by the comment, but has been changed in response to another comment. (See comment 19 above.)

*O. Comments on Testing*

29. One comment recommended that the safety testing guidelines in the Panel's report be retained as guidelines for use only when applicable to a specific antifungal ingredient, as noted in the individual evaluation of that ingredient. The comment stated that requiring a standard battery of safety tests as outlined in the safety testing guidelines (47 FR 12480 at 12559) is appropriate for new drugs but is not appropriate for drugs that have been in widespread use for a long period of time, such as Category III antifungal ingredients. The comment suggested that if there is a particular area of concern for the safety of a given ingredient, then testing should be done in that particular area of concern rather than wasting resources by including testing in areas where safety is well known. Also, the comment pointed out that in several instances the Panel recommended specific tests for certain ingredients.

Another comment contended that, as written, the antifungal guidelines for safety and effectiveness testing are incomplete, confusing, and/or lack feasibility. The comment cited a number of examples to support its contention and recommended that two appropriate scientists from FDA and two from the pharmaceutical industry with experience in antifungal product development review, edit, and finalize these guidelines on laboratory testing.

The agency has not addressed specific testing guidelines in this document. In revising the OTC drug review procedures relating to Category III, published in the **Federal Register** of September 29, 1981 (46 FR 47730), the agency advised that tentative final and final monographs will not include recommended testing guidelines for conditions that industry wishes to upgrade to monograph status. Instead, the agency will meet with industry representatives at their request to discuss testing protocols. The revised procedures also state the time in which test data must be submitted for consideration in developing the final monograph. (See also part II. paragraph A.2. below—*Testing of Category II and Category III Conditions.).*

*P. Comments on Labeling*

30. Three comments disagreed with the use of the term "antifungal" as the required statement of identity on the product label. The comments maintained that antifungal is a technical term that is meaningful to FDA, industry, and health professionals, but may be meaningless to laypersons. The comments suggested that the statement of identify be made more flexible to allow alternative terminology that is more easily understood by consumers to enable them to identify the type of product appropriate for treating a condition they can recognize and self-treat, e.g., "athlete's foot remedy" or "jock itch remedy." Two comments argued that the word "antifungal" was recommended by the Panel as the statement of identity and as such should not have been classified as a Category II labeling statement. Stating that the term is medically correct and meaningful to many consumers, the comments recommended that it be placed in Category I for use elsewhwere on the label, regardless of whether it is also used as a statement of identity.

The agency agrees that the examples of alternative sttements of identity suggested by the comments are understood by consumers, but finds that the terms are similar to the indications statements recommended by the Panel in § 333.250(b) (47 FR 12480 at 12565). The agency sees no need to include in the statement of identity for antifungal drug products the same information found in the indications section. Wherever possible, the agency prefers to use the general pharmacologic category as the statement of identity because information on the principal intended action of the product is provided in the indications section. The agency believes that the indications section is fully informative and will allow consumers to identify the product as being appropriate for a particular condition they wish to self-treat. Therefore, the comment's suggestion is not being proposed in this tentative final monograph. However, the agency has no objection to terms such as "athlete's foot remedy" or "jock itch remedy" appearing elsewhere in the labeling provided they are not intermixed with labeling established by the monograph and do not detract from the required information.

In regard to the Panel's classification of "antifungal" as a Category II labeling claim, the agency concurs with the Panel that " 'antifungal' (when used alone)" in

labeling would be inadequate (47 FR 12480 at 12524) because the term does not provide sufficient information to inform consumers of the particular condition they wish to self-treat. However, the term "antifungal" may be used elsewhere in the labeling, as with the terms "athlete's foot remedy" and "jock itch remedy," discussed above.

31. Two comments asserted that the Panel erroneously expanded the scope of Category II labeling statements (47 FR 12524) by inappropriately including statements that are not "conditions that would result in the drug not being generally recognized as safe and effective or would result in misbranding," but rather are statements describing the performance of the product.

Both comments cited the following Category II claims: "promotes healing," "helps heal," "helps restore normal skin even in severe or persistent cases," "speeds healing of athlete's foot," "speeds healing of jock itch," "kills all major types of athlete's foot fungi," "kills most athlete's foot fungi," and "kills all major types of jock itch fungi." These terms should logically be in Category I, the comments maintained, because the medicinal agent actually kills the fungus and thus allows the infected area to heal. The comments added that this is not the case with many other types of OTC drug products that primarily ameliorate signs and symptoms rather than treat the underlying causes.

One comment added that the claim "for the treatment of athlete's foot and ringworm of the skin, exclusive of bodyfold areas" is simply an accurate statement of the proper use of such products and is not a Category II condition for which the products are not safe and effective.

Because of the comments' assertions, the agency has reevaluated all of the Category II labeling identified by the Panel at 47 FR 12524 for topical antifungal drug products. The agency notes that the Panel considered and classified each claim (that appeared in the labeling of the products that it reviewed) as an indication for use. It should be noted that the OTC drug review program establishes conditions under which OTC drugs are generally recognized as safe and effective and not misbranded. One aspect of the program is to develop standards for certain parts of the labeling of OTC drug products. FDA has found that it is simply not practical—in terms of time, resources, and other considerations—to set standards for all labeling found in OTC drug products. Accordingly, OTC drug monographs directly address only those labeling items that are related in a significant way to the safe and effective use of covered products by lay persons. Those labeling items are the product statement of identity; names of active ingredients; indications for use; directions for use; warnings against unsafe use, side effects, and adverse reactions; and claims concerning mechanism of drug action.

The agency believes that a number of the claims considered by the Panel are descriptive statements that do not relate in a significant way to the safe and effective use of antifungal drug products that are already labeled with the required information, and, therefore, are outside the scope of the monograph. The following claims are included: "athlete's foot, ringworm, jock itch (when these words are used alone)," "antifungal (when used alone)," "kills most athlete's foot fungi," " 'scientific treatment' for athlete's foot," "proven fungicide for athlete's foot, jock itch, and body ringworm fungi," "fungicidal against athlete's foot, jock itch, and ringworm fungi," "broad spectrum antifungal (for treatment of athlete's foot and jock itch)," "kills all major types of athlete's foot fungi," "kills all major types of jock itch fungi," "fungicidal," and "kills fungus spores." The agency believes that such information may be useful to the consumer in describing a product's action or intended effect. However, these and any other terms that are outside the scope of the monograph, even though they are truthful and not misleading, may not be intermixed with labeling established by the monograph and may not detract from the required information. They may be included elsewhere in the labeling.

In contrast, the agency believes that product performance claims such as "kills athlete's foot fungi on contact," "kills athlete's foot on contact," "kills jock itch fungi on contact," "kills athlete's foot fungi fast," "kills jock itch fungi fast," and "for fast relief of itching and burning of athlete's foot and jock itch" are misleading because such claims create a false impression of instant results, while the directions for use of antifungals state that athlete's foot and ringworm products should be used for 4 weeks and jock itch products for 2 weeks. Therefore, these claims remain in Category II.

Claims related to healing, e.g., may promote healing, and wound healing agents are classified as Category III in the rulemaking for OTC skin protectant drug products (48 FR 6820 at 6831; February 15, 1983) and in the rulemaking for OTC anorectal drug products (53 FR 30756 at 30765; August 15, 1988). However, the agency agrees with the comments that antifungal drugs are different from most OTC drug products in that they actually treat the underlying disease rather than only ameliorate signs and symptoms. "Treats," "cures," and "clears up" are included as part of the allowed indications for use in the proposed monograph. The agency believes that labeling that represents or suggests healing, e.g., "promotes healing," "helps heal," "helps restore normal skin even in severe or persistent cases," may be meaningful to the lay person who may consider "heals" and "cures" or "clears up" to be synonymous. Therefore, the agency would allow "helps heal" or "promotes healing" claims to appear elsewhere on the label provided they are not intermixed with labeling established by the monograph. However, data are inadequate to support any product performance claims, e.g., "speeds healing of athlete's foot" and "speeds healing of jock itch." The agency is unaware of any clinical studies for any antifungal ingredient that demonstrates such an effect. Such claims are classified as Category III.

The agency is proposing in this tentative final monograph to classify as Category III claims related to the antibacterial activity of antifungal drug products such as "inhibits growth of fungi and bacteria," "helps prevent ge and fungus infections," "controls bacteria and fungi," "bactericide," "germicide," "antiseptic," and "inhibitory antiseptic," the Panel acknowledged that some Category I antifungal ingredients, i.e., miconazole nitrate and iodochlorhydroxyquin, have in vitro antibacterial activity but concluded that the term "antibacterial" should not be used in labeling of OTC antifungal drug products without supportive clinical studies demonstrating an in vivo antibacterial activity of these ingredients (47 FR 12480 at 12553). The agency agrees with the Panel's recommendation.

The agency is also reclassifying the claims "penetrating action goes under crust and skin surface to kill athlete's foot fungi," "protects broken skin from infection," and "kills all known athlete's foot and jock itch fungi" to Category III because of the lack of data which demonstrate effectiveness for such claims and the lack of data that any Category I ingredient is known to "kill all known" athlete's foot and jock itch fungi.

The agency concludes that the other claims should remain in Category II fo various reasons. "Adjunctive treatment," "for treatment of athlete's foot and ringworm of the skin, exclusive

of body fold areas," and "invisible shield" are unclear and confusing.

Temporary relief of ringworm" and temporary relief of itching and discomfort due to athlete's foot" are inaccurate because Category I antifungal ingredients, when used as directed, provide effective treatment of these conditions, not temporary relief. "The broadest proven dermatophyte spectrum" is not true because Category I antifungals are all effective and are not ranked as good, better, best in the monograph. "Fungistatic" is not true because Category I antifungal ingredients must be fungicidal not just fungistatic.

The agency believes that the term "first aid" is inappropriate in the labeling of a product promoted for the treatment of athlete's foot, jock itch, or ringworm. The term "first aid" is generally perceived as an emergency treatment, and in the context of OTC drug products, for the prevention of infection in minor cuts, scrapes, and burns. (See, e.g., the definition of "first aid antibiotic" in § 333.103(b) of the final monograph for OTC first aid antibiotic drug products (52 FR 47312 at 47323; December 11, 1987).)

Antifungal containing products for "athlete's foot, jock itch, or ringworm" should be used daily for up to 4 weeks and, therefore, are not considered a first aid treatment. The agency agrees with the Panel that the term is misleading and proposes that any claim which represents or suggests an antifungal product is a first aid remedy is Category II labeling.

The Panel recommended that a number of claims be Category II because they are to broad and unspecific to be meaningful. These include: "minor fungus skin infections," "prevention and control of minor skin infections including athlete's foot," "minor skin irritations associated with fungus," "combats and controls infection-causing fungi," "for irritations caused by fungus infections," "for fungus of hands, groin or body," "for superficial fungal infections of the skin," "helps prevent fungal infections," and "guards against fungus growth." The agency believes that these statements standing alone could broaden the intended OTC uses of these products and, therefore, should remain in Category II. However, these descriptive statements, if combined with the conditions for which the product is intended to be used, would be acceptable information for consumers. For example, the following statements would be acceptable: "for irritations caused by athletes foot infections," "for ringworm of hands, groin, or body," and "combats and controls athlete's foot infection-causing fungi." However, any statements that broaden the intended OTC uses of the product would not be acceptable.

A number of claims reviewed by the Panel remain in Category II. The claims "other skin fungus infections," "for the treatment of inflamed conditions of the skin, such as eczema and other fungal infections," and "aids in drying up excessive secretions," remain in Category II because they are too broad and unspecific. These claims imply effectiveness for conditions that are not supported by available data (e.g., eczema or excessive secretions). In addition, when used with the approved monograph indications, those claims that refer to other skin fungus infections may promote self-treatment of fungal infections other than athlete's foot, jock itch, and ringworm.

The claims "clinical improvement was obtained in 88 percent of athlete's foot cases" and "clinical studies show that it cured 78 percent of athlete's foot cases" are also classified as Category II. Specific percentages of successful and unsuccessful treatment will vary according to the test, i.e., an identical product in a different clinical study will result in different findings. All monograph drugs show clinical improvement in a certain percentage of patients. The agency believes that such labeling would not be very meaningful to consumers and could be confusing in selecting which product to use. Therefore, the agency concludes that such labeling should remain in Category II.

32. One comment requested that the statement "this product is not effective on the scalp or nails," which appears in the Panel's recommended directions in § 333.250(d)(1) for products labeled to treat athlete's foot, jock itch, and ringworm, be changed to read "this product is not effective in the treatment of fungal infections of the hair and nails." According to the comment, fungal infections of the skin of the scalp respond just as well to topical agents as does infected skin on other parts of the body.

The Panel provided the following reasons to support its position that topical antifungals are not effective for the treatment of ringworm of the scalp or nails: "Fungal infections of the scalp and nails tend to be chronic. They respond poorly to topical therapy, partly because of the thickness of the nails and the depth of the hair roots. Both sites of infection provide inaccessible locations for fungi, thus drastically decreasing the penetration of topical antifungals." (See 47 FR 12480 at 12487.)

Because the comment did not submit any data to support this suggested change, the agency is retaining the Panel's statement in the directions in this tentative final monograph.

33. Noting its continuing opposition to the exclusivity policy, one comment stated that FDA should not prohibit the use of alternative OTC labeling terminology to describe indications if that terminology is truthful, not misleading, and intelligible to the consumer. The comment stated that the existing statutory provisions (15 U.S.C. 1453(a), 21 CFR 201.61, and sections 502(e) and 508 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352(e) and 358)) do not show a congressional intent to authorize FDA to legislate the exact wording of OTC drug claims to the exclusion of other equally accurate and truthful claims for these products. The comment also stated that if manufacturers use some of the terms recommended by some OTC advisory review panels, their labeling may be in violation of section 502(c) of the act (21 U.S.C. 352(c)), which requires label information to be in such terms as to render it likely to be read and understood by consumers under ordinary conditions of purchase and use. Other comments also stated that it is inappropriate and improper for FDA to prescribe exclusive lists of terms that must be used in labeling.

In the **Federal Register** of May 1, 1986 (51 FR 16258), the agency published a final rule changing its labeling policy for stating the indications of use for OTC drug products. Under 21 CFR 330.1(c)(2), the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either (1) the specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "APPROVED USES"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "APPROVED USES"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "APPROVED USES," plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All other OTC drug labeling required by a monograph or other regulation (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under the OTC drug

monograph or other regulation where exact language has been established and identified by quotation marks, e.g., 21 CFR 201.63 or 330.1(g).

In this tentative final monograph for OTC topical antifungal drug products, supplemental language relating to indications has been proposed and captioned as *Other Allowable Statements.* Under FDA's revised labeling policy (51 FR 16258), such statements are included at the tentative final stage as examples of other truthful and nonmisleading language that would be allowed elsewhere in the labeling. In accordance with the revised labeling policy, such statements would not be included in a final monograph. However, the agency has decided that, because these additional terms have been reviewed by FDA, that should be incorporated, wherever possible, in final OTC drug monographs under the heading "Indications" as part of the indications developed under the monograph.

34. Referring to the Panel's guidelines for effectiveness studies and effectiveness standards for labeling indications of antifungal drug products for the treatment of ringworm of the body (47 FR 12480 at 12562), one comment disagreed with the Panel and stated that the treatment period should be 2 weeks and not 4 weeks with followup studies at 2 weeks and 4 weeks. The comment requested that the Panel's recommended directions in § 33.250(d)(1) be revised to provide for a 2-week treatment period of ringworm of the body rather than the 4-week period recommended by the Panel. The comment also requested that the directions be revised to alert consumers that "if a ringworm infection of the body does not clear within 2 weeks, professional consultation is recommended."

As discussed in comment 29 above, specific testing requirements are not being addressed in this tentative final monograph. With regard to the directions for use of antifungal drug products for the treatment of ringworm of the body, the Panel stated in its report that "The dosing regimen is standardized. Athlete's foot and ringworm are more difficult to treat than jock itch. For this reason the treatment period should be at least 4 weeks for athlete's foot and ringworm and 2 weeks for jock itch" (47 FR 12480 at 12492). The comment gave no reasons for changing the treatment period from 4 weeks to 2 weeks and did not submit any data to support its request. Thus, the agency concurs in the Panel's recommendation. Until data to support the comment's requests are submitted and evaluated, the changes recommended by the comment will not be made.

35. Several comments objected to the agency's dissent from the Panel's recommendation that certain prescription to OTC antifungal drugs be labeled "for the treatment of external itching associated with vaginal yeast (candidal) infections." One of the comments contended that "properly labeled anti-yeast and anti-inflammatory agents can be used safely and with benefits as OTC products." Another comment pointed out that 0.5 percent hydrocortisone for OTC use has an approved indication for the temporary relief of itching around the vagina.

After reconsidering its intention to include OTC antifungal drug products labeled for the treatment of external feminine itching in this rulemaking, the agency believes that it would be more appropriate to defer the consideration of antifungals for this labeling claim to the rulemaking for OTC vaginal drug products. (See the **Federal Register** of October 13, 1983; 48 FR 46694 at 46695 and 46729.) Therefore, comments on this subject that were submitted to the rulemaking for OTC antifungal drug products will be incorporated into the rulemaking for OTC vaginal drug products. If any antifungal ingredient is determined to be appropriate for the relief of external vaginal itching, it will be considered in the rulemaking for OTC vaginal drug products. The same antifungal ingredient may be determined to be appropriate for the prevention and/or treatment of athlete's foot and the treatment of ringworm and jock itch and will remain in the rulemaking or OTC antifungal drug products for this indication.

In the tentative final monograph for OTC external analgesic drug products, the agency proposed that hydrocortisone and hydrocortisone acetate 0.25 to 0.5 percent be available OTC for temporary relief of "genital" or "feminine" itching. (See the **Federal Register** of February 8, 1983; 48 FR 5852.) Thus, some of the concerns that the agency raised in the rulemaking for OTC antifungal drug products in 1982 were subsequently addressed in the external analgesic rulemaking. The agency will present its final conclusions on this use of hydrocortisone in the final monograph for OTC external analgesic drug products in a future issue of the **Federal Register.**

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

### *A. Summary of Ingredient Categories and Testing of Category II and Category III Conditions*

1. *Summary of ingredient categories.* The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and is proposing to reclassify povidone-iodine (10 percent) from Category III to Category I and phenol (less than or equal to 1.5 percent) from Category II to Category III. The agency is also proposing to reclassify nystatin from Category I to Category III. As a convenience to the reader, the following list is included as a summary of the categorization of topical antifungal active ingredients recommended by the Panel and the categorization proposed by the agency.

| Topical antifungal active ingredients | Panel | Agency |
|---|---|---|
| Aluminum salts | III | III |
| Alcioxa | | |
| Aluminum sulfate | | |
| Potassium alum | | |
| Basic fuchsin | III | III |
| Benzethonium chloride | III | III |
| Benzoic acid | III | III |
| Borates | III | |
| Boric acid | | |
| Sodium borate | | |
| Camphor | II | II |
| Candicidin | II | II |
| Caprylates | III | III |
| Sodium caprylate | | |
| Zinc caprylate | | |
| Chlorothymol | III | III |
| Chloroxylenol | III | III |
| Clioquinol (Iodochlorhydroxyquin) | I | I |
| Coal tar | II | II |
| Cresols | III | III |
| Camphorated metacresol | | |
| *m*-Cresol | | |
| Secondary amyltricresols | | |
| Dichlorophen | III | III |
| Haloprogin | I | I |
| Menthol | II | II |
| Miconazole nitrate | I | I |
| Nystatin | I | III |
| Oxyquinolines | III | III |
| Benzoxiquine | | |
| Oxyquinoline | | |
| Oxyquinoline sulfate | | |
| Parabens | III | III |
| Methylparaben | | |
| Propylparaben | | |
| Phenolates | II | III |
| Phenol | | |
| Phenolate sodium | | |
| Phenyl salicylate | III | III |
| Povidone-iodine | III | I |
| Propionic acid and its salts | III | III |
| Sodium propionate | | |
| Zinc propionate | | |
| Resorcinol | II | II |
| Salicylic acid | III | III |
| Sulfur | III | |
| Tannic acid | II | |
| Thymol | II | |
| Tolindate | II | |
| Tolnaftate | I | I |

| Topical antifungal active ingredients | Panel | Agency |
|---|---|---|
| Triacetin | III | III |
| Undecylenic acid and its salts | I | I |
| Calcium undecylenate | | |
| Copper undecylenate | | |
| Zinc undecylenate | | |

2. *Testing of Category II and Category III conditions.* The Panel recommended testing guidelines for topical antifungal drug products in 47 FR 12480 at 12558. The agency's position regarding the Panel's testing guidelines is discussed in comment 29 above. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any topical antifungal ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the **Federal Register** of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). That policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

*B. Summary of the Agency's Changes*

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the Panel's report and recommended monograph with the changes described in FDA's responses to the comments above and with other changes described in the summary below. A summary of the changes made by the agency follows.

1. The agency has revised the definition of dermatophyte in § 333.203 to read: "A fungus that invades and lives upon the skin or in the hair or nails." (See comment 6 above.) The agency has also revised the definition of jock itch in § 333.203 to read: "A chronic and recurrent dermatophyte infection which affects the upper, inner thighs and sometimes extends to the groin and the pubic area; the condition most frequently occurs in men, but may also occur in women."

2. The agency has reclassified phenol from Category II to Category III. (See comment 12 above.)

3. The agency has reclassified povidone-iodine 10 percent into Category I. (See comment 14 above.)

4. The wording of § 333.250(b)(2) has been revised to be consistent with the style and format of § 333.250(b)(1), thereby including tolnaftate by reference rather than by name. (See comment 19 above.)

5. The Panel recommended that two or three antifungal ingredients identified in § 333.210 be combined provided each ingredient broadens the antifungal spectrum and provided the product is labeled according to § 333.250(b)(1). Because the Category I antidermatophytic antifungal ingredients have very similar spectra and combinations of up to three of these ingredients would result in duplication with respect to target organisms (that cause athlete's foot, jock itch, and ringworm) rather than broaden the antifungal activity, the agency is not proposing these combinations in this tentative final monograph. These combinations are classified in Category III in this document. (See comment 24 above.)

6. The agency is not proposing that any single active ingredient identified in § 333.210 or any combination of antifungal active ingredients be allowed in combination with an antiperspirant active ingredient for the treatment of athlete's foot, jock itch, and ringworm. These combinations are classified in Category III in this document. (See comment 22 above.)

7. The agency is not proposing that combinations of up to three Category I antifungal ingredients and hydrocortisone or hydrocortisone acetate 0.5 to 1 percent be available for OTC use in the treatment of athlete's foot, jock itch, and ringworm. The agency is deferring classification of such combinations in this rulemaking until the DESI proceeding involving one specific combination (clioquinol/hydrocortisone) is completed. (See comment 23 above.)

8. Because of the lack of efficacy data and a concern about safety of such products, the agency is not proposing combinations of Category I antifungal ingredients and any single keratolytic agent that is generally recognized as safe and effective in an OTC drug final monograph. These combinations are classified in Category III in this document. (See comment 26 above.)

9. The agency believes that it is more appropriate to defer the consideration of antifungal ingredients for treatment of external feminine itching to the rulemaking for OTC vaginal drug products. If any antifungal ingredient is determined to be appropriate for the relief of external vaginal itching, it will be considered in the rulemaking for OTC vaginal drug products. (See comment 35 above.)

10. The agency has determined that it is more appropriate to discuss the entire subject of diaper rash at one time. The comments on diaper rash drug products submitted to this rulemaking will be addressed at a later date when OTC diaper rash products are evaluated. (See comment 5 above.)

11. In the absence of information showing that infection by *Candida albicans* is a significant cause of athlete's foot or jock itch or that secondary infections of *Candida* are common in these conditions, the agency is not proposing the combination of an antidermatophytic ingredient with an anticandidal ingredient such as nystatin. Accordingly, the agency is reclassifying nystatin used in combination with other antifungal ingredients from Category I to Category III. (See comments 8 and 24 above.)

12. The agency is not including nystatin as a single Category I antifungal ingredient in this tentative final monograph. The Panel placed nystatin in Category I for the treatment of vaginal and superficial skin infections caused by *Candida albicans*. Because the agency has decided to defer the external feminine itching issue to another rulemaking and has determined that treatment of superficial skin infections caused by yeast (*Candida*) is not an appropriate OTC claim, nystatin as a single ingredient is not included in this tentative final monograph. (See comments 8, 24, and 35 above.)

13. The agency has concluded that no OTC antifungal drug product ingredient may be labeled for the treatment of cutaneous candidiasis, but that such claims may be included in the professional labeling for these products. Therefore, the agency is moving the labeling recommended by the Panel in § 333.250(b)(4) to the professional labeling section of this tentative final monograph. (See comment 8 above.)

14. No combinations are being proposed in this tentative final monograph. Therefore, the Panel's recommended § 333.220 is not being included in this tentative final monograph. (See comments 22 through 28 above.)

15. The agency has reevaluated all of the Category II labeling identified by the Panel and changed the status of certain claims. (See comment 31 above.)

16. The agency is not proposing the labeling for product attributes recommended by the Panel in § 333.250(b)(8). The Panel recommended that terms used to describe certain physical and chemical qualities of a drug product may be used in the labeling as long as these terms do not imply any therapeutic effect and are distinctly separated from the indications statements. These terms, such as "greaseless" or "nonstaining," are intended to provide consumer

information and relate to a product's color, odor, or feel. OTC drug monographs regulate only labeling information related in a significant way to those therapeutic properties of covered products having a direct bearing on their safe and effective use by lay persons. Claims concerning nontherapeutic characteristics of drugs, such as product attributes, are not dealt with in OTC drug monographs. Such terms may not appear in any portion of the labeling that is required by the monograph, but may appear elsewhere in the labeling. Labeling claims of this type are, however, subject to the misbranding provisions of the act.

17. In several places in the warnings and directions sections, the Panel recommended that the consumer consult a doctor or pharmacist if certain conditions occur. These included: (1) If irritation occurs or if there is no improvement within 2 or 4 weeks, (2) if the condition persists or recurs, (3) do not use longer than 30 days, and (4) if satisfactory results have not occurred within these times (2 or 4 weeks' use of the antifungal product). Although the pharmacist is an important member of the health care team, FDA believes that the situations covered by these warnings and directions are more appropriately handled by the physician. In cases where there is no improvement or the condition persists or recurs, diagnosis of the condition by the physician is necessary to determine the actual nature of the condition and the appropriate treatment. It is likely in such cases, where the OTC drug product has not provided satisfactory relief, that the physician will treat the patient with a prescription medication. Therefore, the agency is not including the word pharmacist, as recommended by the Panel, in these warnings and directions as proposed in this tentative final monograph.

18. In the warnings section, the agency is proposing the statement "Avoid contact with the eyes" in addition to the warning "For external use only" recommended by the Panel. Use of both statements is consistent with the warnings included in a number of other OTC drug monographs for topical drug products. (See, for example, the tentative final monograph for OTC external analgesic drug products (48 FR 5852; February 8, 1983); the tentative final monograph for OTC skin protectant drug products (48 FR 6820; February 15, 1983); and the final monograph for OTC topical otic drug products (51 FR 28658; August 8, 1986).)

19. In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs to substitute the word "doctor" for "physician" in OTC drug monographs on the basis that the word "doctor" is more commonly used and better understood by consumers. Based on comments to these proposals, the agency has determined that final monographs and any applicable OTC drug regulations will give manufacturers the option of using either the word "physician" or the word "doctor." This tentative final monograph proposes that option. (See § 333.250(e) below.)

20. Under agency regulations relating to official names and established names for drugs in § 299.4(b) (21 CFR 299.4(b)), the established name of a drug is defined in section 502(e) of the act (21 U.S.C. 352(e)) as (1) an official name designated pursuant to section 508 of the act (21 U.S.C. 358); (2) if no such official name has been designated for the drug and the drug is an article recognized in an official compendium, then the official title thereof in such compendium; and (3) if neither paragraphs (1) or (2) applies, then the common or usual name for the drug. "Iodochlorhydroxyquin" and 'Clioquinol" are synonyms for the same chemical entity for which an official name has not been designated pursuant to section 508 of the act. However, "Clioquinol" is the official title in an official compendium (Ref. 1) and therefore is the established name; accordingly "Iodochlorhydroxyquin" in § 333.210(b) of the Panel's recommended monograph has been replaced with "Clioquinol" in § 333.210(a) of this tentative final monograph.

Reference

(1) "The United States Pharmacopeia XXI—The National Formulary XVI," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 227, 1985.

21. For products containing clioquinol, the agency is proposing the following warnings: "Do not use on children under 2 years of age" and "Do not use for diaper rash." These statements must appear in bold face type as the first warnings under the "Warnings" heading. (See Citizen Petition below.)

## III. Citizen Petition

On July 24, 1985, a Citizen Petition was filed urging FDA to remove from the market as dangerous to infants and adults all prescription and OTC drugs containing clioquinol (formerly named iodochlorhydroxyquin) (Ref. 1). The petition stated that these drugs, when applied directly to the skin, are used in many cases for diaper rash and other skin problems in infants and children. The oral form of clioquinol was previously used to treat travelers' diarrhea and a rare disease known as acrodermatitis enteropathica. This form of the drug was taken off the market in most countries, including the United States, because it was linked to over 10,000 cases of subacute myelo-opticoneuropathy (SMON) in Japan and other countries.

While no cases of SMON related to the dermatologic use of clioquinol have been reported, the petition stated that there is now reason to believe that the topical form of the drug poses a significant threat of toxicity. According to the petition, recent studies have demonstrated that there is substantial percutaneous absorption of clioquinol resulting from topical use in humans and dogs, and that amounts of the drug not excreted from the body are stored in tissue. Further, it contended that animal studies suggest that toxicity may occur at fairly low levels of exposure, levels close to those an infant may receive. The petition expressed the view that clioquinol is dangerous because it concentrates in the organs and can cause SMON and liver toxicity. In support of its views, the petition cited recently published studies by Stohs et al. (Ref. 2) and Ezzedeen et al. (Ref. 3). (Those studies were published after publication of the Panel's report and thus were not evaluated by the Panel.)

In the Stohs study (Ref. 2), 5 gram (g) doses of 3 percent clioquinol cream were applied to the forearms of five healthy male subjects. Each dose was applied over a 200 square centimeter ($cm^2$) area, and the entire area was occluded with plastic wrap. Blood and urine samples were collected and assayed regularly. Twelve hours after application, the remaining drug was removed from the subjects' forearms. The amount removed was quantitatively analyzed and, based on this analysis, the authors concluded that approximately 40 percent of the topically applied drug had been absorbed.

In the Ezzedeen study (Ref. 3), 5 g doses of 3 percent clioquinol cream were applied twice daily to the backs of five mongrel dogs. The cream was applied over a shaved 200 $cm^2$ area and occluded with plastic wrap. The applications were continued for 28 days. Blood samples were drawn and assayed for clioquinol on a regular basis. The percentage of drug absorbed was estimated by measuring the amount of drug remaining on the back of each dog. Using this unvalidated method, the authors estimated that approximately 52 percent of the drug was absorbed.

This study was primarily a percutaneous absorption study.

However, the authors also made several observations that they suggest are toxic effects related to topical treatment with clioquinol. One dog died after 15 days of topical treatment, and microscopic examination of the liver revealed necrosis. One dog developed partial hand limb paralysis similar to that reported in a Japanese study of oral administration of clioquinol (Ref. 4). However, histologic and neurologic evaluations of this dog were not performed. All treated dogs lost weight, while no weight loss occurred in control animals.

In the second phase of this study, in addition to the topical application of clioquinol, three dogs were injected with a 100 milligrams (mg) intravenous (IV) bolus dose of clioquinol 2 months after topical treatment. The three dogs were killed 2 weeks after the bolus injections. Liver, kidney, and mesenteric adipose tissues were analyzed for clioquinol, and mean levels of 1.22, 0.83, and 0.88 mg/g, respectively, were found. The authors also microscopically examined the liver tissues of the 3 dogs and found liver lesions similar to those found in the dog that died after 15 days of topical treatment. The control dogs were not sacrificed or examined similarly.

The petition contended that if 1 g of a 3-percent clioquinol preparation was applied to a child's diaper rash three times a day, a total daily dose of 90 mg per day would be applied. If the child weighed 10 kilograms (kg) (22 lbs), the amount of clioquinol would be 9 mg/kg/day, which is close to the 17 mg/kg/day dose in the dog study and over three times higher than the single dose of 2.5 mg/kg in the human study in which blood levels of 0.37–0.56 mg/milliliter (mL) were obtained. The petition also expressed concern about the 9 mg/kg/day an infant might receive because of its proximity to the oral doses received by SMON victims (many between 12.5 and 25 mg/kg/day).

On November 18, 1985, FDA's Dermatologic Drugs Advisory Committee met to consider the petition. Sidney J. Stohs, a principal investigator in both cited studies, appeared before the Committee and discussed the results of his work.

After extensive questioning and discussion, the Committee generally agreed that the two studies upon which the petition is largely based are not adequate to support the removal of all clioquinol products from the market. The Committee expressed concern however that absorption of the drug by infants, even in small amounts, poses a potential risk, and voted to recommend that clioquinol be moved from the OTC market to prescription status to prevent indiscriminate use of the drug, especially in infants (Ref. 5).

The agency has reviewed the data presented in the petition. With regard to the Stohs' study (Ref. 2), the agency is unable to conclude that the extent of percutaneous absorption was reliably established. The method used to determine the extent of absorption is an indirect method of determining the absorption of topically applied drugs and, to the agency's knowledge, has not been validated as an accurate method. The published report on this study does not provide any information regarding the validity of this method. Furthermore, at the November 1985 Dermatologic Drug Advisory Committee meeting (Ref. 5), Dr. Stohs was unable to provide assurance that the method had been validated as accurate. The agency believes that it is highly probable that this method will greatly overestimate the amount of drug absorbed because of the difficulty in removing all of the drug remaining on the skin.

The agency believes that the observations made during the topical application phase of the Ezzedeen study are of concern, but also believes that the evidence linking the effects observed to the drug is weak. The published paper provides no information documenting that the pretreatment status and the handling of the dogs during the study were comparable for the treatment and control groups. Furthermore, at the November 1985 Dermatologic Drugs Advisory Committee meeting (Ref. 5), Dr. Stohs, one of the investigators in the Ezzedeen study, stated that the treatment and control dogs were not handled in a similar fashion.

The agency also finds the toxicity and tissue retention observations concerning the three dogs that received IV injections of clioquinol inadequate to support a conclusion that topical application of the drug would cause similar effects. The relationship between the effects of IV clioquinol administration and the effects of topical clioquinol application is unknown. Moreover, because of the inadequate control procedures used, the liver toxicity observations cannot be confidently attributed to the IV administration of clioquinol.

Overall, the agency believes that the two studies primarily relied upon to support the petition are inadequate to demonstrate that OTC topical clioquinol, prescription topical clioquinol/hydrocortisone, and prescription topical clioquinol/nystatin are dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in their labeling. Based upon the extensive marketing history of this ingredient, the agency concludes that there are insufficient data available to justify removing all clioquinol-containing drug products from the market as misbranded under section 502(j) of the act (21 U.S.C. 352(j)) based upon the information presented in the petition.

Although the agency does not believe that the existing information requires removal of topical clioquinol from the market as suggested by the petition, or restriction to prescription-only status as recommended by the Dermatologic Drugs Advisory Committee, the agency shares the concern expressed by the petition and the Advisory Committee that use of topical clioquinol on infants may potentially place them at increased risk. This risk is not well defined because of the lack of information relating to the use of topical clioquinol on infants.

The Antimicrobial II Panel evaluated possible blood levels and the potential toxicity resulting from several "worst case" situations in which clioquinol would be applied topically to broken skin. The Panel considered application to a jock itch or ringworm condition, both of which represent a larger surface area than an athlete's foot condition, and assumed total and rapid absorption occurs after each application. The Panel reported that the blood levels estimated from such exposure would be well below the reported 15-to-30 μg/mL blood levels obtained during a 2-week oral administration of clioquinol in which no toxic symptoms were observed. (See 47 FR 12480 at 12496.)

In an adult, the surface area of contact is small (probably less than 5 percent) when clioquinol is used for its approved OTC indications. If clioquinol were used for diaper rash in infants, the affected area may be 10 to 15 percent of the body surface. Additionally, inflamed and often open surface areas are more permeable and permit a greater degree of absorption. Clioquinol is detoxified in the adult liver by conjugation with a glucuronide. Infants do not have as fully developed a conjugation pathway as adults; thus, clioquinol may accumulate in infants due to a reduced ability to detoxify the drug. Additionally, a young child has less percent body fat and a developing nervous system. Although clioquinol is not specifically approved for diaper dermatitis and there are no known reports of SMON or major systemic toxicity in children following topical use, children under age 2 are on theoretical grounds the population with the highest potential risk for an adverse outcome. Accordingly, while the agency

believes that clioquinol may remain on the OTC market labeled for its approved OTC uses (i.e., athlete's foot, jock itch, and ringworm), it must be labeled that it is not for use on children under 2 years of age and that it is not for use for diaper rash. Therefore, the agency is proposing that 2 warning statements appear on all OTC drug products containing clioquinol, and that these statements appear in bold face type as the first warnings on the label, as follows: "Do not use on children under 2 years of age." "Do not use for diaper rash."

References

(1) Citizen Petition, Public Citizen Health Research Group, July 24, 1985, Coded CP, Docket No. 85P–0344, Dockets Management Branch.

(2) Stohs, S. J., et al., "Percutaneous Absorption of Iodochlorhydroxyquin in Humans," *The Journal of Investigative Dermatology*, 82:195–198, 1984.

(3) Ezzedeen, F. W., et al., "Percutaneous Absorption and Disposition of Iodochlorhydroxyquin in Dogs," *Journal of Pharmaceutical Sciences*, 73:1369–1372, 1984.

(4) Kono, R. "Introductory Review of Subacute Myelo-optico Neuropathy (SMON) and Its Studies Done by the SMON Research Commission," *Japanese Journal of Medical Science and Biology (Supp.)*, 28:1–21, 1975.

(5) Summary Minutes of the 26th Meeting of the Dermatologic Drugs Advisory Committee, November 18, 1985.

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 antifungal drug products, 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 antifungal drug products 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 antifungal drug products. No comments on economic impacts were received. Any comments on the agency's initial determination of the economic consequences of this proposed rulemaking should be submitted by March 11, 1990. 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 carefully considered the potential environmental effects of this action. FDA has concluded that the action will not have a significant impact on the human environment, and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday. This action was considered under FDA's final rule implementing the National Environmental Policy Act (21 CFR part 25).

The agency is proposing to remove § 310.201(a)(29) because the conditions in that section for tolnaftate preparations will be superseded by the requirements of the final monograph on OTC antifungal drug products (subpart C of 21 CFR part 333).

Interested persons may, on or before March 11, 1990, submit to the Dockets Management Branch written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before March 11, 1990. 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, objections, 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 December 12, 1990, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before February 2, 1991. 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 (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 monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on February 12, 1991. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register**, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

List of Subjects

*21 CFR Part 310*

Administrative practice and procedure, Drugs, Medical devices, Reporting and recordkeeping requirements.

*21 CFR Part 333*

Antifungal drug products, Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act, it is proposed that subchapter D of chapter I of title 21 of the Code of Federal Regulations be amended in parts 310 and 333 as follows:

## PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

**Authority:** Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512–516, 520, 601(a), 701, 704, 705, 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 376); secs. 215, 301, 302(a), 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b–263n).

**§ 310.201 [Amended]**

2. Section 310.201 *Exemption for certain drugs limited by new-drug*

*applications to prescription sale* is amended by removing paragraph (a)(29).

## PART 333—TOPICAL ANTIMICROBIAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

3. The authority citation for 21 CFR part 333 continues to read as follows:

**Authority:** Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

4. Part 333 is amended by adding new subpart C to read as follows:

### Subpart C—Topical Antifungal Drug Products

Sec.
333.201 Scope.
333.203 Definitions.
333.210 Antifungal active ingredients.
333.250 Labeling of antifungal drug products.
333.280 Professional labeling.

### Subpart C—Topical Antifungal Drug Products

#### § 333.201 Scope.

(a) An over-the-counter antifungal drug product in a form suitable for topical administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this subpart and each general condition established in § 330.1 of this chapter.

(b) References in this subpart to regulatory sections of the Code of Federal Regulations are to chapter I of title 21 unless otherwise noted.

#### § 333.203 Definitions.

As used in this subpart:

(a) *Antifungal.* A drug which inhibits the growth and reproduction of fungal cells and decreases the number of fungi present.

(b) *Athlete's foot.* An infection of the feet caused by dermatophytic fungi.

(c) *Dermatophyte.* A fungus that invades and lives upon the skin or in the hair or nails.

(d) *Fungus.* Any of a large division of plants, including dermatophytes, yeasts, and molds, characterized by a simple cell structure and the absence of chlorophyll.

(e) *Jock itch.* A chronic and recurrent dermatophyte infection which affects the upper, inner thighs and sometimes extends to the groin and the pubic area; the condition most frequently occurs in men, but may also occur in women.

(f) *Ringworm.* A skin infection caused by dermatophytic fungi.

#### § 333.210 Antifungal active ingredients.

The product consists of any of the following active ingredients within the specified concentrations established for each ingredient and the product is labeled according to § 333.250.

(a) Clioquinol 3 percent.

(b) Haloprogin 1 percent.

(c) Miconazole nitrate 2 percent.

(d) Povidone-iodine 10 percent.

(e) Tolnaftate 1 percent.

(f) Undecylenic acid, calcium undecylenate, copper undecylenate, and zinc undecylenate may be used individually or in any ratio which provides a total undecylenate concentration of 10 to 25 percent.

#### § 333.250 Labeling of antifungal drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "antifungal."

(b) *Indications.* The labeling of the product states, under the heading "Indications," any of the phrases listed in this paragraph, as appropriate. Other truthful and nonmisleading statements describing only the indications for use that have been established in this paragraph (b), may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) *For products containing any ingredient idenified in § 333.210 labeled for the treatment of athlete's foot, jock itch, and ringworm.* (Select one of the following: "Treats," "For the treatment of," "For effective treatment of," "Cures," "For the cure of," "Clears up," or "Proven clinically effective in the treatment of") (select one condition from any one or more of the following groups of conditions: (i) "athlete's foot," "athlete's foot (dermatophytosis)," "athlete's foot (tinea pedis)," or "tinea pedis (athlete's foot)"; (ii) "jock itch," "jock itch (tinea cruris)," or "tinea cruris (jock itch)"; or (iii) "ringworm," "ringworm (tinea corporis)," or "tinea corporis (ringworm).")

(2) *For products containing the ingredient identified in § 333.210(e) labeled for the prevention of athlete's foot.* (Select one of the following: "Clinically proven to prevent," "Prevents," "Proven effective in the prevention of," "Helps prevent," "For the prevention of," "For the prophylaxis (prevention) of," "Guards against," or "Prevents the recurrence of") (select one of the following: "athlete's foot," "athlete's foot (dermatophytosis)," "athlete's foot (tinea pedis)," or "tinea pedis (athlete's foot)") "with daily use."

(3) *Other allowable statement for products labeled according to paragraph (b)(1) of this section.* The labeling of the product may contain an additional indication statement as follows: (Select one of the following: "Relieves," "For relief of," "For effective relief of," or "Soothes,") (select one or more of the following: "itching," "scaling," "cracking," "burning," "redness," "soreness," "irritation," "discomfort," "chafing associated with jock itch," "itchy, scaly skin between the toes," or "itching, burning feet").

(4) *Other allowable statement for products labeled according to paragraph (b)(2) of this section.* The labeling of the product may contain an additional indication statement as follows: "Clears up athlete's foot infection and with daily use helps keep it from coming back."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For products containing any ingredient identified in § 333.210.* (i) "Do not use on children under 2 years of age except under the advice and supervision of a doctor."

(ii) "For external use only."

(iii) "Avoid contact with the eyes."

(2) *For products labeled according to paragraph (b)(1) of this section for the treatment of athlete's foot and ringworm.* "If irritation occurs or if there is no improvement within 4 weeks, discontinue use and consult a doctor."

(3) *For products labeled according to paragraph (b)(1) of this section for the treatment of jock itch.* "If irritation occurs or if there is no improvement within 2 weeks, discontinue use and consult a doctor."

(4) *For products labeled according to paragraph (b)(2) of this section for the prevention of athlete's foot.* "If irritation occurs, discontinue use and consult a doctor."

(5) *For products containing the ingredient identified in § 333.210(a) labeled according to paragraph (b)(1) of this section.* The following statements must appear in bold face type as the first warnings under the "Warnings" heading. (i) "Do not use on children under 2 years of age." (This warning is to be used in place of the warning in paragraph (c)(1)(i) of this section.)

(ii) "Do not use for diaper rash."

(d) *Directions.* The labeling of the product contains the following statements under the heading "Directions:"

(1) *For products labeled according to paragraph (b)(1) of this section for the treatment of athlete's foot, jock itch, and ringworm.* "Cleanse skin with soap and water and dry thoroughly. Apply" (the

word "spray" may be used to replace the word "apply" for aerosol products) "a thin layer over affected area morning and night or as directed by a doctor. For athlete's foot, pay special attention to the spaces between the toes. It is also helpful to wear well-fitting, ventilated shoes and to change shoes and socks at least once daily. Best results in athlete's foot and ringworm are usually obtained with 4 weeks' use of this product, and in jock itch, with 2 weeks' use. If satisfactory results have not occurred within these times, consult a doctor. Children under 12 years of age should be supervised in the use of this product. This product is not effective on the scalp or nails."

(2) *For products labeled according to paragraph (b)(2) of this section for the prevention of athlete's foot.* "To prevent fungal infection of the feet (athlete's foot), cleanse skin with soap and water and dry thoroughly. Apply" (the word "spray" may be used to replace the word "apply" for aerosol products) "a thin layer to feet once or twice daily, paying special attention to the toenails and the spaces between the toes. It is also helpful to wear well-fitting, ventilated shoes and to change shoes and socks at least once daily."

(e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this section.

**§ 333.280 Professional labeling.**

The labeling provided to health professionals (but not to the general public) may contain the following additional indication:

(a) *For products containing haloprogin or miconazole nitrate identified in § 333.210 (a) and (c).* "For the treatment of superficial skin infections caused by yeast (*Candida albicans*)."

(b) [Reserved]

Dated: October 28, 1989.

**James S. Benson,**

*Acting Deputy Commissioner of Food and Drugs.*

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