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; Final Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing 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 final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and all new data and information on OTC topical antifungal drug products that have come to the agency's attention. This final monograph is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: September 23, 1994.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD–810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5000.

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 (the Panel), 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 accordance with § 330.10(a)(10), the data and information considered by the Panel, after deletion of a small amount of trade secret information, were placed on display in the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857.

The agency's proposed regulation, in the form of a tentative final monograph, for OTC topical antifungal drug products was published in the **Federal Register** of December 12, 1989 (54 FR 51136). Interested persons were invited to file by April 11, 1990 written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal. Interested persons were invited to file comments on the agency's economic impact determination by April 11, 1990. New data could have been submitted until December 12, 1990, and comments on the new data could have been submitted until February 12, 1991.

In the **Federal Register** of September 7, 1982 (47 FR 39464) the agency published an advanced notice of proposed rulemaking to establish conditions under which OTC topical antifungal drug products used for the treatment of diaper rash were generally recognized as safe and effective and not misbranded. The agency also reopened the administrative record for this rulemaking for OTC topical antifungal drug products to allow for consideration of a statement on topical antifungal drug products used for the treatment of diaper rash that had been received from the Advisory Review Panel on OTC Miscellaneous External Drug Products. Interested persons were invited to submit comments until December 6, 1982, and reply comments by January 5, 1983. The agency discussed topical antifungal drug products for the treatment or prevention of diaper rash in a notice of proposed rulemaking published in the **Federal Register** of June 20, 1990 (55 FR 25240). A final rule was published in the **Federal Register** of December 18, 1992 (57 FR 60430). No topical antifungal active ingredients were generally recognized as safe and effective for OTC use for the treatment or prevention of diaper rash. (See 21 CFR 310.545(a)(22)(i).)

In the **Federal Register** of September 2, 1993 (58 FR 46744), the agency issued a final rule establishing that certain labeling claims for OTC topical antifungal drug products, i.e., for use on the scalp or on the nails, are not generally recognized as safe and effective and are misbranded. (See 21 CFR 310.545(a)(22)(iii).)

The OTC drug procedural regulations (§ 330.10) 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 does not 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. In place of Category I, the term "monograph conditions" is used; in place of Category II or III, the term "nonmonograph conditions" is used.

As discussed in the proposed regulation for OTC topical antifungal drug products (54 FR 51136 at 51137), the agency advised that the conditions under which the drug products that are subject to this monograph will be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication in the **Federal Register**. Therefore, on or after September 23, 1994, 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. This 12-month effective date does not apply to OTC topical antifungal drug products for the treatment or prevention of diaper rash or for use on the scalp or the nails. The effective date for the final rule for topical antifungal drug products for the treatment or prevention of diaper rash was June 18, 1993. The effective date for the final rule for topical antifungal drug products for use on the scalp and nails is March 2, 1994.

In response to the proposed rule on OTC topical antifungal drug products, one law firm, one drug manufacturers association, and four drug manufacturers submitted comments. Copies of the comments received are on public display in the Dockets Management Branch (address above). Additional information that has come to the agency's attention since publication of the proposed rule is also on public

display in the Dockets Management Branch.

I. The Agency's Conclusions on the Comments

A. General Comment

1. One comment mentioned that in May 1989 an FDA spokesperson had disclosed that the agency would be "liberalizing" its prior policy and would allow simultaneous marketing of separate prescription and OTC versions of the same pharmaceutical entity in the same strength and dosage form. The comment stated that the agency spokesperson indicated that this change in policy would be announced in the **Federal Register**, and that comments would be requested. The comment noted that on October 27, 1989, the agency approved the OTC marketing of the antifungal drug clotrimazole for three of its former prescription indications, but allowed another manufacturer to continue to market the same drug in the same dosage form and strength for the same three indications on a prescription basis. The comment stated that no **Federal Register** notice of the new policy had been published to date and wanted to know the agency's timetable for publishing such a notice.

The approval for OTC marketing of the antifungal drug clotrimazole occurred under new drug applications (NDA's) and was not part of this rulemaking proceeding. Likewise, the policy, and any possible **Federal Register** notice discussing that policy, that the comment mentioned is not part of this rulemaking proceeding and will not be discussed further in this document. (It should be noted that the "other" product mentioned by the comment was subsequently approved for OTC marketing status under an NDA.)

B. Comment on Combination Products

2. Two comments supported the agency's statements in the tentative final monograph (comment 24, 54 FR 51136 at 51150) concerning the rationality of combinations of antifungal ingredients, from a theoretical and medical standpoint, if such combinations were: (1) Shown to have increased antifungal spectra; or (2) provided concurrent treatment of multiple symptoms, e.g., an antifungal ingredient combined with an analgesic, anesthetic, or antipruritic ingredient. One comment urged the agency to remain receptive to the submission of any new clinical data that support such combinations.

In the tentative final monograph, the agency did not propose any combinations of Category I antifungal ingredients, but instead classified in Category III various combinations recommended by the Panel. (See comments 22 through 28, 54 FR 51136 at 51148 through 51153.) Neither comment submitted any data to support any combination products. Resolution of the status of clioquinol-hydrocortisone combination products is currently pending in a Drug Efficacy Study Implementation proceeding outside of this rulemaking. A formal evidentiary hearing concluded in March 1986 and an Administrative Law Judge (ALJ) Initial Decision was issued on February 5, 1988, stating there is a lack of substantial effectiveness of the combination product and ordering NDA's for such products withdrawn. Exceptions to the Initial Decision and Replies to the Exceptions have been filed and are pending resolution in that forum. Based on the ALJ Initial Decision, such a combination product would not be included in the monograph. This was discussed in the tentative final monograph. (See comment 23, 54 FR 51136 at 51149.)

Thus, all antifungal combination products are nonmonograph in this final rule. However, the agency remains receptive to the submission of any new clinical data that would support general recognition of the safety and effectiveness of such combination products.

C. Comments on Labeling

3. One comment requested evaluation of a protocol for a clinical study designed to determine the effectiveness of undecylenates in the prevention of athlete's foot (Ref. 1). The protocol was for a 12-week, double-blind, parallel group study with approximately 90 subjects each per test drug and placebo.

The agency evaluated the protocol and found that it essentially complied with the Panel's guidelines for this type of study but needed a few modifications. The agency's detailed comments on the evaluation of this protocol are on file in the Dockets Management Branch (address above) (Ref. 2).

Subsequently, the comment responded to the agency's recommendations and agreed to the suggested modifications of the protocol (Ref. 3). The agency has not received any further communications from the comment regarding this study protocol, nor has it received any study results. Accordingly, at this time the claim for prevention of athlete's foot for undecylenates is nonmonograph in this final rule for OTC topical antifungal drug products. When the study results are available, they may be submitted in the form of a petition to amend the final monograph in accord with § 330.10(a)(12).

References

(1) Comment No. C00026, Docket No. 80N–0476, Dockets Management Branch.

(2) Letter from W.E. Gilbertson, FDA, to J. L. Miller, Fison's Pharmaceuticals, Coded LET22, Docket No. 80N–0476, Dockets Management Branch.

(3) Comment No. SUP3, Docket No. 80N–0476, Dockets Management Branch.

4. One comment submitted two studies (Refs. 1 and 2) to show that miconazole nitrate 2 percent (in a powder dosage form) is effective in preventing athlete's foot. One study (Ref. 1) was a double-blind, comparative study in which 198 subjects were randomly assigned to 4 weeks of treatment with 1 of 3 powder products: Miconazole nitrate, zinc undecenoate (zinc undecylenate) and undecenoic acid (undecylenic acid), or placebo. There was a 4-week followup period. The second study (Ref. 2) was a 12-week, double-blind, multicenter study with 28 subjects randomly assigned to treatment with either a 2-percent miconazole nitrate powder, a vehicle control (100 percent talcum powder), or no active medication treatment. The comment believed that this study met the criteria established by the Panel and that it demonstrated a significant difference in effectiveness of the miconazole nitrate treated subjects remaining symptom-free over the vehicle-control and the no-treatment subjects, at the end of the 12-week trial.

The agency evaluated these studies and determined that they had a number of defects and are not sufficient to demonstrate the effectiveness of miconazole nitrate 2 percent for the prevention of athlete's foot. First, there was an insufficient number of subjects to evaluate the statistical significance of the data reported in the studies. Second, in one study (Ref. 2), causative organisms were not identified for all subjects, no key was provided for the clinical data to determine which medication was given to each subject, and a 1-percent miconazole nitrate powder was listed on the clinical case report forms, not 2 percent. Third, in the other study (Ref. 1), the treatment groups were not separated, and the rate of infection/reinfection was not reported for the antifungal treatments individually. Finally, there was no significant difference demonstrated in the clinical cure rate between the three groups at 8 weeks. The agency's detailed comments on the evaluation of these studies are on file in the Dockets Management Branch (address above)

(Ref. 3). The agency has not received any further communication regarding its evaluation of these studies, nor have any additional supportive data been submitted. Accordingly, the claim for prevention of athlete's foot for miconazole nitrate 2 percent is nonmonograph in this final rule for OTC topical antifungal drug products. If a study supportive of a prevention of athlete's foot claim for this drug becomes available, it may be submitted in the form of a petition to amend the final monograph in accord with § 330.10(a)(12).

References

(1) Edwards, H.W., "The Treatment of Chronic Athletes' Foot: A Possible Role for Prophylaxis," British Journal of Clinical Practice, pp. 5–7, 1978.

(2) "Clinical Prophylaxis Study of Miconazole Nitrate 2 Percent (Powder) in Comparison to the Vehicle (100 Percent Talcum Powder) and to No Preventative Medication in the Treatment of Tinea Pedis," unpublished study submitted by Advanced Care Products, Ortho Pharmaceutical Corp., Comment C00029, Docket No. 80N–0476, Dockets Management Branch.

(3) Letter from W.E. Gilbertson, FDA, to J.R. Grieve, Advanced Care Products, Ortho Pharmaceutical Corp., coded LET25, Docket No. 80N–0476, Dockets Management Branch.

5. One comment requested that miconazole nitrate 2 percent be permitted an OTC labeling indication for the topical treatment of superficial candidiasis (yeast infections) associated with athlete's foot and jock itch. The comment disagreed with the agency's proposal to limit the anticandidal claim to professional labeling only (54 FR 51136 at 51140). The comment cited the Panel's conclusion that miconazole nitrate was effective in the treatment of external itching associated with vaginal yeast infection and superficial skin infections caused by yeast (*Candida*), plus the Panel's recommendation of Category I status for such indications (47 FR 12480 at 12501). The comment also mentioned the Panel's statement that a combination product containing an antidermatophytic and anticandidal ingredient would offer broader therapy (47 FR 12554). The comment noted the agency's disagreement with the Panel's OTC labeling recommendation (54 FR 51140) but felt that the agency had not stated a reason for not allowing this claim in OTC labeling for athlete's foot products. The comment argued that there was no public health reason not to allow an indication for OTC treatment of yeast infections associated with athlete's foot. The comment added that it is not necessary that a consumer be diagnosed or cultured by a physician in order to treat athlete's foot.

The comment noted the agency's statements in the tentative final monograph (54 FR 51151) regarding the absence of information showing that *Candida* is a significant cause of athletes' foot or jock itch, or that secondary infections with *Candida* are common. The comment added that, although the agency classified the combination of an antidermatophytic and an anticandidal ingredient in Category III, the agency stated that it would consider the combination if data were submitted demonstrating that *Candida* is a significant problem in dermatophytic infections. The comment provided published studies (Refs. 1 through 11) to show that yeasts are commonly recognized in association with superficial dermatophytic infections and are often a secondary cause of infection.

The agency has reviewed the submitted studies and determined that they do not provide convincing epidemiological data that *Candida* or yeasts are a significant problem in cases of dermatophytic infections seen in the United States. Only 3 of the 11 studies (Refs. 2, 4, and 11) dealt with superficial fungal infections in the United States, but none of these studies were large enough to have epidemiologic value. Also, in the cases of *Tinea pedis* presented in the studies, no clear distinction was made between the plantar type, where *Candida* would not be expected, and the intertriginous type, where *Candida* might be expected.

The study by Fulton (Ref. 2) was a drug efficacy study done in a south Florida prison population using 99 males 20 to 29 years old with endemic fungal disease. *Candida* was isolated in 11 subjects, while *Trichophyton rubrum* and *Candida* were isolated in 3 subjects. The study was done during hot, humid, summer weather and may not be representative of the fungal pathogens found in the general U.S. population. The emphasis of the study was on therapy, not epidemiology; the demographic characteristics of the population were restricted to a limited range, not representative of the U.S. population; and the number of subjects was too small to be considered as an epidemiological study to establish the presence of candidiasis associated with athlete's foot.

The study by Leyden and Kligman (Ref. 4) concerned the interaction of dermatophytes and resident bacteria in interdigital athlete's foot and provided little support toward the comment's claim. *Candida albicans* was not isolated in any of the 4 test groups, but *Candida* species were isolated in 9 (18.7 percent) of 48 normal subjects, in 1 (2.6 percent) of 39 subjects classified as dermatophytosis simplex, in 5 (11.6 percent) of 43 subjects classified as dermatophytosis complex, and in 4 (6.7 percent) of 58 subjects classified as severe macerated dermatophytosis complex.

The study by Terleckyj, Goldman, and Abramson (Ref. 11) determined the fungal and bacterial flora of the toe webs in 29 subjects with athlete's foot compared to a control group of 25 noninfected volunteers. The etiologic agents in 51 percent of the athlete's foot subjects were shown to be dermatophytes (31 percent), C. albicans (10 percent), and *Staphylococcus aureus* (10 percent), but no single definitive agent was demonstrated in the remaining 49 percent of the *C. albicans* subjects. The emphasis of this study was the bacterial population of the interdigital space in subjects with athlete's foot compared to normal, noninfected control subjects. The study indicated that definitive evidence implicating *Candida* species as a primary cutaneous foot pathogen was lacking; the significance of *Candida* in athlete's foot was not demonstrated. Moreover, the number of subjects in the study was too small to be of epidemiological use.

Five of the studies were conducted in India, where the distribution of fungal pathogens may not reflect that of the U.S. population. In one study (Ref. 1) 3,500 cases with superficial fungal infections were studied among military personnel at various sites in India, where many differences that exist may influence the distribution of fungal pathogens, and thus may not reflect conditions in the United States. Two studies (Refs. 3 and 9) reported on a variety of superficial mycoses. The authors of one study (Ref. 9) noted that superficial mycoses are worldwide and are quite common in India. However, the dermatophytes that cause the common superficial infections differ from place to place and their prevalence is governed by environmental conditions, personal hygiene, and individual susceptibility. *Candida* species were isolated in a small number (less than 10 percent) of subjects. The authors commented that while *C. albicans* seems to be quite a prevalent species, it is difficult to comment about its primary pathogenic ability to produce lesions. Pankajalakshimi et al. (Ref. 8) reported on the incidence of *T. pedis* in a local population in India in 217 randomly selected subjects. The study was undertaken because the incidence of *T. pedis* is very low in India, which was attributed to a large number of people who walk barefoot

because of the warm climate and their low income. The study showed that infection rates varied in different geographical areas of India. Pathogenic fungi were found in the interdigital spaces of the feet in 15.2 percent of the subjects with clinical abnormality (32.7 percent), and in 1.8 percent of the individuals with normal conditions. *T. rubrum* was the major offender (42.4 percent), followed by *C. albicans* (27.3 percent) and *Trichophyton mentagrophytes* (24.2 percent). The incidence of *C. albicans* varied from 8.3 to 66.7 percent, which the investigators believed to be due to the causative species differing from place to place and from time to time. Thus, the agency has concerns whether the study results would apply in the United States. Talwar et al. (Ref. 10) studied 96 subjects for the prevalence of bacteria and fungi in athlete's foot of varying severity. The authors indicated that *Candida* seemed to play a role in the pathogenesis of athlete's foot because a higher percentage of *Candida* species was found in subjects with moderate and severe disease, compared to those with mild disease. The authors also stated, however, that warm weather, sweating, and maceration may play a role in the increased number of *Candida* isolates seen in this Indian study, as compared to the insignificant number isolated in the 140 subjects with athlete's foot in the U.S. study by Leyden and Kligman (Ref. 4). The study supports the contention that studies conducted in India may not reflect the distribution of fungal pathogens in the U.S. population. In addition, from an epidemiologic perspective, this was a small study.

McAleer (Ref. 5) reported that during a 10-year period, from 1963 to 1972, 1,154 fungal infections of the feet were diagnosed in Western Australia from examination of 2,732 subjects. Dermatophytic fungi were responsible for 75.6 percent, and *Candida* species were responsible for 24.2 percent of the infections. Like the Indian studies, this report provides little support for the comment's claim because the data from Western Australia may not reflect the distribution of fungal pathogens in the U.S. population. The author mentioned a number of factors that provided an opportunity to contract fungal infections of the feet: (1) A Mediterranean-type climate; (2) a shoe-wearing population; (3) frequent showering; (4) use of public bathing facilities; and (5) the habits and way of life of individuals concerned. The agency is also concerned that because the data were gathered over 20 years ago, the information may not represent the distribution of fungal pathogens today.

A textbook chapter on candidiasis of the skin (Ref. 7) provided little information on *Candida* in athlete's foot, except to state that *Candida* lesions between the fingers and toes are easily confused with dermatophytosis. However, in this chapter, under the heading "Incidence and distribution of lesions," it is stated that "Forman diagnosed 70 cases of candidiasis of skin and nail among 14,008 new cases (0.5 percent) in a British hospital for skin diseases." The agency finds this to be a very low incidence rate. Further, among the cases of *Candida* reported, intertrigo, the groins, and the perianal region were most commonly affected, followed by the axillae, then the submammary regions. This information does not support the presence of *Candida* in athlete's foot. Another chapter from a textbook on podiatric dermatology (Ref. 6) provided little in the way of epidemiological support. It stated that *C. albicans* can mimic the clinical symptoms of athlete's foot and can be isolated, but no information was provided regarding how frequently it is isolated.

The submitted studies have not shown that yeasts (*Candida*) play a significant role in athlete's foot in the U.S. population. Many species of fungi, yeasts, and bacteria may be present, but consumers have no way of distinguishing whether *Candida* is present and is a causative microorganism. At this time, there is not an adequate basis to include in the final monograph an additional OTC (consumer) labeling indication for miconazole nitrate 2 percent for topical treatment of superficial yeast infections associated with athlete's foot. However, should sufficient data be submitted to show that *Candida* is generally prevalent in subjects with dermatophytic infections that occur in the U.S. population, the agency will consider amending the final monograph to include such a claim in the OTC (consumer) labeling.

Products containing miconazole nitrate 2 percent may state in their professional labeling (information provided to health professionals, but not to the general public) that the product can be used "for the treatment of superficial skin infections caused by yeast (*Candida albicans*)." This allows health professionals to recommend these products to consumers, who can then purchase them OTC when the presence of *Candida* has been established as a cause of the infection. This professional labeling appears in new § 333.280(a) of this final monograph.

References

(1) Anand, L.C., U.K. Singh, and B.S. Rathore, "Fungal Flora in the Armed Forces: Clinical and Mycological Studies," Indian Journal of Medical Research, 71:365–371, 1980.

(2) Fulton, J.E., Jr., "Miconazole Therapy for Endemic Fungal Disease," Archives of Dermatology, III(5):596–598, 1975.

(3) Jacob, Z. et al., "Superficial Mycoses and in Vitro Sensitivity of Dermatophytes and Candida Species to Tolciclate and Clotrimazole," Indian Journal of Medical Research, 74:365–371, 1981.

(4) Leyden, J.J., and A.M. Kligman, "Interdigital Athlete's Foot," Archives of Dermatology, 114:1466–1472, 1978.

(5) McAleer, R., "Fungal Infection as a Cause of Skin Disease in Western Australia, I Tinea Pedis," Australasian Journal of Dermatology, 22:80–84, 1981.

(6) McCarthy, D.J., editor, "Dermatophytosis and Atopy," in Podiatric Dermatology, Williams and Wilkins, Baltimore, pp. 139–141, 1986.

(7) Odds, F.C., "Candidiasis of the Skin, Nails, and Other External Sites," in Candida and Candidiasis, University Park Press, Baltimore, pp. 113–120, 1979.

(8) Pankajalakshimi, V.V. et al., "Incidence of Tinea Pedis Among the Local Population in Madras," Indian Journal of Dermatology, Venereology, and Leprology, 46:209–215, 1980.

(9) Talwar, P. et al., "Study of Human Dermatomycosis," Indian Journal of Medical Research, 70:187–194, 1979.

(10) Talwar, P. et al., "Prevalence of Bacteria and Fungi in Athlete's Foot of Varying Severity and Response to Topical Antibacterial and Antifungal Therapies," Sabouraudia: Journal of Medical and Veterinary Mycology, 23:303–312, 1985.

(11) Terleckyj, B., S.M. Goldman, and C. Abramson, "Microflora of the Intertriginous Toe Surfaces of Patients with Athlete's Foot," Journal of the American Podiatry Association, 71(10):529–535, 1981.

6. Two comments disagreed with the agency's Category II classification of claims regarding speed of symptomatic relief and onset of fungicidal activity for OTC antifungal drug products. The comments contended that claims such as "kills athlete's foot fungi fast," "kills athlete's foot fungi on contact," and "for fast (or speedy) relief of itching and burning of athlete's foot and jock itch" are performance claims and should be included among the claims acknowledged by the agency to be outside the scope of the monograph (54 FR 51136 at 51154). The comments added that these claims should be permitted, provided they are scientifically substantiated.

The comments disagreed with the agency's characterization of these claims as misleading (54 FR 51154) and argued that there was no evidence showing that

consumers are misled or confuse fast symptomatic relief with fast resolution of the underlying condition. The comments added that the label directions make clear to consumers the length of treatment necessary for curing the fungal infection. The comments asked the agency to reconsider this issue and handle it as was done in the tentative final monograph for OTC external analgesic drug products (48 FR 5852 at 5861, February 8, 1983) where the agency recognized terms such as "fast," "prompt," "swift," "sudden," and "immediate" as not related significantly to the safe and effective use of these products and determined that such terms were outside the scope of the monograph. The comments requested that these claims not be considered as indications, but be permitted as additional labeling statements that are allowed elsewhere in the labeling.

The types of claims described as performance claims by the comments were among the claims determined to be unacceptable by the Panel (47 FR 12480 at 12524). The Panel placed claims of this type in Category II because they were unsupported by scientific data or were considered vague, too broad, incomplete, or modified incorrectly. In the tentative final monograph for OTC antifungal drug products, the agency reevaluated all of the Category II labeling identified by the Panel (47 FR 12524). The agency acknowledged that certain claims were 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 considered outside the scope of the monograph (54 FR 51136 at 51154). On the other hand, the agency specifically identified certain performance claims, like those discussed by the comments, which it considered misleading and as creating a false impression of instant results, because the directions for use state that the product should be used for 4 weeks for athlete's foot and ringworm and for 2 weeks for jock itch. Therefore, the agency proposed that performance claims of this type remain in Category II (54 FR 51154).

The comments specifically mentioned that performance claims of this type should be allowed if substantiated by scientific data. However, neither the Panel nor the agency is aware of any scientific data to support such claims. If adequate data are submitted to support this type of claim, the agency will consider including such claims in the monograph. In this case, where the drug is to be used for 2 or 4 weeks, the agency believes that the words "fast" or "speedy," if used in the product's labeling, need to be defined and put into context, based on valid scientific data. The agency does not find this situation to be similar to its decision on the labeling of these terms for OTC external analgesic drug products because those products are intended to be used for 7 days or less.

After reconsidering the issues raised by the comments, the agency finds, in the absence of supporting data, that claims regarding speed of symptomatic relief and onset of fungicidal activity provided by antifungal drug products are nonmonograph in this final rule for OTC topical antifungal drug products. If scientific data become available substantiating these claims, they may be submitted in the form of a petition to amend the final monograph in accord with §§ 10.30 (21 CFR 10.30) and 330.10(a)(12).

7. One comment requested that the agency shorten the warning statement proposed in § 333.250(c)(1)(i) (21 CFR 333.250(c)(1)(i)), which reads: "Do not use on children under 2 years of age except under the advice and supervision of a doctor." The comment's suggested version reads: "Do not use on children under 2 years of age except on the advice of a doctor." The comment stated that its version contains all the relevant information for safe and effective use of OTC antifungal drug products and conserves scarce label space.

The agency agrees with the comment that the warning statement can be shortened. The agency has looked at similar warning statements in other OTC drug monographs and determined that the warning "Do not use on children under 2 years of age unless directed by a doctor" is most consistently used in these monographs. (See, for example, the final monographs for OTC antiemetic drug products (§ 336.50 (c)(2) through (c)(5) (21 CFR 336.50 (c)(2) through (c)(5)) and cold, cough, allergy, bronchodilator, and antiasthmatic drug products § 341.74 (c)(4)(iii) and (c)(4)(iv) (21 CFR 341.74 (c)(4)(iii) and (c)(4)(iv)); and the tentative final monographs for OTC skin bleaching drug products (September 3, 1982, 47 FR 39108), OTC internal analgesic drug products (November 16, 1988, 53 FR 46204), and OTC antidiarrheal drug products (April 30, 1986, 51 FR 16138).) Accordingly, the agency is revising this warning in this final monograph to read: "Do not use on children under 2 years of age unless directed by a doctor."

8. One comment suggested deletion of the warning in proposed § 333.250(c)(1)(iii) that states, "Avoid contact with the eyes." The comment stated that the eye area is not an affect area to which these products are appl for labeled uses.

The agency disagrees with the comment's suggestion to delete this warning. Even though some of the labeled uses (athlete's foot and jock itch) for OTC antifungal drug products involve areas of the body remote from the eye, another labeled use (ringworm) may involve facial areas close to the eyes. Further, regardless of the area treated, antifungal drugs are usually applied with the fingers, and a consumer may inadvertently touch the eye area if not warned to avoid contact with the eyes. After applying the drug to the affected area, fingers can become contaminated by the microorganisms causing athlete's foot, jock itch, and ringworm. In addition, drug products used in the eye are required to be sterile (free of all microorganisms); drug products for topical use do not have this requirement, and thus the product itself may contain microorganisms that can contaminate the eye and cause infection. Accordingly, the agency is retaining the warning "Avoid contact with the eyes" in this final monograph for OTC topical antifungal drug products.

9. One comment objected to the agency's proposal in § 333.250 (c)(2), (c)(3), and (c)(4) of the tentative final monograph that deleted "pharmacist" from the Panel's recommended warnings, which stated: "If irritation occurs or if there is no improvement within 4 [or 2] weeks, discontinue use and consult a doctor or pharmacist," or "If irritation occurs, discontinue use and consult a doctor." The comment stated that pharmacists are health-care professionals who are readily available to consumers and should not be overlooked as a source for providing advice directly to consumers. The comment added that it is possible that removal of "pharmacist" from the warnings would result in a consumer who needs advice not consulting a health professional at all. The comment mentioned that there have been no known untoward effects from having "pharmacist" included in these warnings for over 8 years (since the advance notice of proposed rulemaking was published in 1982).

The agency discussed this issue in the tentative final monograph (54 FR 51136 at 51158) and noted that 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, * * *. The agency stated that although the

pharmacist is an important member of the health-care team, FDA believes that the situations covered by these warnings are more appropriately handled by a physician. Conditions that do not improve, persist, or recur should be diagnosed by a physician to determine the exact nature of the condition and the appropriate treatment. Although the agency acknowledges that the pharmacist is an important health-care professional, it is likely in such cases that where the OTC drug product has not provided satisfactory relief, the physician will treat the patient with a prescription medication. The agency disagrees that a consumer who needs advice would not consult a health professional at all if the word "pharmacist" is not included in the warnings. The comment provided no data to support this contention and most surveys show that pharmacists are routinely consulted by consumers for advice. Accordingly, the agency is not including "pharmacist" in the warnings in § 333.250 (c)(2), (c)(3), and (c)(4) in this final monograph for OTC topical antifungal drug products.

10. Two comments suggested deletion of the direction statement proposed in § 333.250(d)(1), which states: "Children under 12 years of age should be supervised in the use of this product." One comment stated that while this is a common sense advisory, it knew of no reason why it should apply to antifungals as opposed to any other topical drug products. The other comment gave no specific reason for recommending the deletion of this statement other than to shorten the directions in general.

The agency disagrees with the comments' suggestion to delete this direction statement, but believes that it can be shortened to read: "Supervise children in the use of this product." The agency points out that direction statements of this type are included in several tentative final monographs for OTC topical oral drug products. (See, for example, the tentative final monographs for oral mucosal injury drug products (July 26, 1983, 48 FR 33984 at 33993), anticarious drug products (September 30, 1985, 50 FR 39854 at 39872 and 39873), oral health care drug products (January 27, 1988, 53 FR 2436 at 2460 and 2461), and oral health care drug products amendment to include relief of oral discomfort drug products (September 24, 1991, 56 FR 48302 at 48343 through 48346).)

The agency believes that there are good reasons why children need supervision in applying topical antifungal drug products. The other portions of the directions discussed in comment 12 state specific procedures that should be followed as to washing and drying the affected area, the amount of drug to apply, and the time of application. Children under 12 years of age may not be able to read or understand the labeling directions or may not follow them correctly without adult supervision. Accordingly, the agency is including a revised direction statement in this final monograph that reads: "Supervise children in the use of this product."

11. One comment suggested deletion of the direction statement in proposed § 333.250(d)(1), which states: "This product is not effective on the scalp or nails." The comment stated that there is nothing in the indications that would suggest use on the scalp or nails.

The agency disagrees with the comment's suggestion to delete this statement. The agency included this statement in the tentative final monograph based on the Panel's statements that fungal infections of the scalp and nails tend to be chronic. Such infections respond poorly to topical therapy, partly because of the thickness of the nails and the depth of the hair roots. Both the scalp and nails provide inaccessible locations for fungi, thus drastically decreasing the penetration of topical antifungals. For those reasons, the Panel recommended that OTC topical antifungal drug products must be labeled that they are not effective for the treatment of ringworm of the scalp or nails (47 FR 12480 at 12487).

The agency is aware that claims for use on the scalp and nails have appeared in antifungal drug product labeling over the years. However, insufficient evidence has been submitted to establish that any OTC topical antifungal drug product is effective for the treatment of fungal infections on the scalp and on the nails. The agency concluded that such uses for OTC topical antifungal drug products were not generally recognized as safe and effective in the **Federal Register** of September 2, 1993 (58 FR 46744). Accordingly, the agency is retaining the statement "This product is not effective on the scalp or nails" in § 333.250(d)(1) of this final monograph for OTC topical antifungal drug products.

12. Two comments stated that the agency's proposed directions in § 333.250(d)(1) were unnecessarily lengthy. These directions read:

> 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.

The comments recommended shortened directions. One comment stated that the following version includes the important directions for safe and effective consumer use in easily understood language:

> Wash and dry affected areas thoroughly. Apply [spray] product liberally to affected areas twice daily or as directed by a doctor. For athlete's foot, apply liberally especially to spaces between the toes. For athlete's foot or ringworm, continue to use daily for 4 weeks. For jock itch, use daily for 2 weeks. If condition persists longer consult a doctor. This product is not effective on the scalp or nails.

The other comment stated that the following version contains all the relevant information for safe and effective use of OTC antifungal drug products, and conserves scarce label space:

> *For Athlete's Foot Indication.* Wash and dry feet thoroughly. Apply [spray] product liberally to affected areas twice daily or as directed by a doctor. For athlete's foot, apply liberally to spaces between the toes. For athlete's foot and [ringworm] continue to use daily for 4 weeks. If condition persists longer consult a doctor. *For Jock Itch Indication.* Wash and dry affected area. Apply product to affected area twice daily or as directed by a doctor. Continue to use daily for 2 weeks. If condition persists longer, consult a doctor.

The agency agrees with the comments that the directions can be shortened. The agency has looked at similar direction statements in other OTC drug monographs for topical drug products and determined that certain direction statements, such as "Wash [cleanse] the affected areas and dry thoroughly" and "apply a small amount, or thin layer," are most consistently used in these monographs, while other direction statements are specific for the drug product category. See, for example, the final monographs for OTC corn and callus remover drug products (§ 358.550 (d)(1) and (d)(2) (21 CFR 358.550 (d)(1) and (d)(2)), wart remover drug products (§ 358.150 (d)(1) through (d)(3) (21 CFR 358.150 (d)(1) through (d)(3)), first aid antibiotic drug products (§ 333.150 (d)(1) through (d)(3) (21 CFR 333.150 (d)(1) through (d)(3)), topical acne drug products (§ 333.350(d)(1) (21 CFR 333.350(d)(1)), and anorectal drug products (§ 346.50(d)(1) (21 CFR 346.50(d)(1)). Based on these directions,

the agency is providing the option of using the word "clean" or "wash" the affected area.

The agency is retaining the statement "apply a thin layer * * * morning and night" because it is not aware of any data that support the need to "apply liberally" as the comments recommend. Using liberal amounts of a topical antifungal drug is not necessarily better, and if the product is not a cream or a spray dosage form, liberal application may cause maceration due to moisture accumulating beneath the layer of drug. Further, standard compendia recommend applying small amounts for some antifungals twice daily, morning and night (Refs. 1, 2, and 3). Indicating the time of application (morning and night) is more specific than twice daily by itself and helps avoid possible consumer misuse. Consumers could interpret twice daily as a few hours apart, resulting in a nonuniform time between applications. Also, it is more convenient for consumers to apply the drug after washing and drying the affected area in the morning before dressing and in the evening after undressing. Therefore, while retaining "morning and night" as the times when to apply, the agency is adding "twice daily" as how often to apply, as recommended by the comments, to the directions.

The agency is also retaining the statements recommended by the Panel regarding changing shoes and socks daily because some fungal infections can be prevented and others terminated through control of the local environment and improvement in the patient's hygiene. As noted by the Panel, fungal infections are difficult to establish naturally on normal dry skin, and skin damage and increased moisture (from tight shoes, excessive sweating, humid weather, etc.) contribute to the development and continuation of athlete's foot and jock itch (47 FR 12480 at 12488).

The direction statement regarding the use of antifungal drug products on children under 12 years of age is discussed in comment 10. The use of antifungal drug products on the scalp or nails is discussed in comment 11.

Accordingly, after considering the comments' recommendations and the labeling in other monographs for OTC topically applied drug products, the agency is revising the directions in this final monograph to read:

[Select one of the following: "Clean" or "Wash"] "the affected area and dry thoroughly. Apply" (the word "spray" may be used to replace the word "apply" for aerosol products) "a thin layer of the product over affected area twice daily (morning and night) or as directed by a doctor. Supervise children in the use of this product. For athlete's foot: Pay special attention to spaces between the toes; wear well-fitting, ventilated shoes, and change shoes and socks at least once daily. For athlete's foot and ringworm, use daily for 4 weeks; for jock itch, use daily for 2 weeks. If condition persists longer, consult a doctor. This product is not effective on the scalp or nails."

References

(1) "Topical Anti-Infective Agents: Drugs used on Skin and Mucous Membranes," in AMA Drug Evaluations, 6th ed., American Medical Association, Chicago, pp. 1513–1516, 1986.

(2) "Drug Information for the Health Care Professional," vol. I, 13th ed., United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 1937 and 2724, 1993.

(3) "Advice for the Patient," vol. II, 13th ed., United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 371, 691, 900, 1330, and 1349, 1993.

13. One comment recommended a shortened version of the directions proposed in § 333.250(d)(2), which state:

"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 spaces between the toes. It is also helpful to wear well-fitting, ventilated shoes and to change shoes and socks at least once daily."

The comment's suggested shortened directions read: "To prevent athlete's foot, apply liberally to clean, dry feet, especially to spaces between the toes." The comment contended that it was not necessary or a desirable use of scarce label space to give protracted directions on good foot hygiene and common sense footcare in the instructions for use of a drug product. The comment stated that its version retained the important substantive statements in shortened language.

The agency agrees with the comment that the directions for prevention of athlete's foot can be shortened. However, as with the directions for treatment of athlete's foot, the agency has determined that certain direction statements, such as "apply a thin layer," and information about wearing well-fitted, ventilated shoes should be retained. (See comment 12.) The agency notes that the comment's shortened directions do not provide the time of application of the drug product for prevention of athlete's foot. The agency is providing the option of using the word "clean" or "wash" the skin and is retaining the "once or twice daily" concept, but is adding the statement "morning and/or night" because it provides consumers useful information about the most convenient times of the day to apply the product. (See comment 12.) The agency is adding the statement "Supervise children who use this product," (see comment 10), and the agency is deleting the word "toenails" because topical antifungal drug products have not been shown to be effective for fungal infections of the nails. (See comment 11.)

Accordingly, after considering the comment's and the Panel's recommendations, the agency is revising the directions in this final monograph for antifungal drug products indicated for prevention of athlete's foot to read:

"To prevent athlete's foot," (select one of the following: "clean" or "wash") "the feet and dry thoroughly. Apply" (the word "spray" may be used to replace the word "apply" for aerosol products) "a thin layer of the product to the feet once or twice daily (morning and/or night). Supervise children in the use of this product. Pay special attention to spaces between the toes; wear well-fitting, ventilated shoes, and change shoes and socks at least once daily."

II. Summary of Changes From the Proposed Rule

1. The agency is shortening the warning proposed in § 333.250(c)(1)(i) to read: "Do not use on children under 2 years of age unless directed by a doctor." (See comment 7.)

2. The agency is revising the directions for products labeled for the treatment of athlete's foot, jock itch, and ringworm to read:

[Select one of the following: "Clean" or "Wash"] "the affected area and dry thoroughly. Apply" (the word "spray" may be used to replace the word "apply" for aerosol products) "a thin layer of the product over affected area twice daily (morning and night) or as directed by a doctor. Supervise children in the use of this product. For athlete's foot: Pay special attention to spaces between the toes; wear well-fitting, ventilated shoes, and change shoes and socks at least once daily. For athlete's foot and ringworm, use daily for 4 weeks; for jock itch, use daily for 2 weeks. If condition persists longer, consult a doctor. This product is not effective on the scalp or nails." (See comments 10 and 12.)

3. The agency is revising the directions for products labeled for the prevention of athlete's foot to read:

"To prevent athlete's foot," (select one of the following: "clean" or "wash") "the feet and dry thoroughly. Apply" (the word "spray" may be used to replace the word "apply" for aerosol products) "a thin layer of the product to the feet once or twice daily (morning and/or night). Supervise children in the use of this product. Pay special attention to spaces between the toes; wear well-fitting, ventilated shoes, and change shoes and socks at least once daily." (See comment 11.)

4. In order to allow for greater lexibility in indications statements, the agency is revising and expanding proposed § 333.250 (b)(1) and (b)(2) to incorporate as additional optional indications the other allowable statements that were proposed in § 333.250 (b)(3) and (b)(4). Proposed § 333.250(b)(3) is redesignated as § 333.250(b)(1)(ii) and proposed § 333.250(b)(4) is redesignated as § 333.250(b)(2)(ii) in this final monograph.

5. The agency is clarifying the definitions of athletes' foot, jock itch, and ringworm in § 333.203 (b), (e), and (f), respectively, by adding the word "certain" to state that these infections are only caused by certain dermatophytic fungi.

III. The Agency's Final Conclusions on OTC Topical Antifungal Drug Products

Based on available evidence, the agency is issuing a final monograph establishing conditions under which OTC topical antifungal drug products are generally recognized as safe and effective and not misbranded. Specifically, the agency has determined that the only ingredients that meet monograph conditions are clioquinol, haloprogin, miconazole nitrate, povidone-iodine, tolnaftate, undecylenic acid, calcium undecylenate, copper undecylenate, and zinc undecylenate. All other ingredients considered in this rulemaking have been determined to be nonmonograph for use in a topical antifungal drug product. These ingredients include, but are not limited to, alcloxa, aluminum sulfate, basic fuchsin, benzethonium chloride, benzoic acid, benzoxiquine, boric acid, camphor, camphorated metacresol, candicidin, chlorothymol, chloroxylenol, coal tar, *m*-cresol, dichlorophen, menthol, methylparaben, nystatin, oxyquinoline, oxyquinoline sulfate, phenol, phenolate sodium, phenyl salicylate, potassium alum, propionic acid, propylparaben, resorcinol, salicylic acid, secondary amyltricresols, sodium borate, sodium caprylate, sodium propionate, sulfur, tannic acid, thymol, tolindate, triacetin, zinc caprylate, and zinc propionate.

The agency has established 21 CFR 310.545 in which are listed certain active ingredients that are not generally recognized as safe and effective for certain OTC drug uses. That regulation includes in § 310.545(a)(22)(iii) any topical antifungal active ingredients labeled with claims or directions for use on the scalp or on the nails. The effective date of § 310.545(a)(22)(iii) is March 2, 1994. That regulation also includes in § 310.545(a)(22)(i) any topical antifungal active ingredients labeled with claims or directions for use in the treatment and/or prevention of diaper rash. The effective date for § 310.545(a)(22)(i) was June 18, 1993. That regulation also includes in § 310.545(a)(22)(ii) a number of topical antifungal active ingredients for which no significant comments or new data were submitted to upgrade their status and which were finalized as nonmonograph at an earlier date. (See the **Federal Register** of May 10, 1993, 58 FR 27636.) The agency is adding § 310.545(a)(22)(iv) to include the remaining nonmonograph antifungal active ingredients considered as part of this rulemaking for OTC antifungal drug products. The comments and new data on these ingredients are addressed in this final rule. The effective date for § 310.545(a)(22)(iv) is September 23, 1994.

Accordingly, any drug product labeled, represented, or promoted for use as an OTC topical antifungal that contains any of the ingredients or labeling listed in § 310.545 (a)(22)(i) through (a)(22)(iv) or that is not in conformance with the monograph (21 CFR part 333, subpart C) may be considered a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)) and misbranded under section 502 of the act (21 U.S.C. 352) and cannot be marketed for this use unless it is the subject of an approved application under section 505 of the act (21 U.S.C. 355) and part 314 of the regulations (21 CFR part 314). An appropriate citizen petition to amend the monograph may also be submitted under § 10.30 in lieu of an application. Any OTC topical antifungal drug product initially introduced or initially delivered for introduction into interstate commerce after the effective dates listed above that is not in compliance with the regulations is subject to regulatory action. 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.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (54 FR 51136 at 51160). The agency has examined the economic consequences of this final rule 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 final rule for OTC topical 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 topical antifungal drug products is not expected to pose such an impact on small businesses. This final rule will require some reformulation and/or relabeling. Products that currently contain monograph ingredients will only need to be relabeled, and manufacturers will have 1 year to implement this relabeling. Based on information provided by a nonprescription drug manufacturers' association, the estimated average cost of a labeling revision is about $2,000.00 per product label. Products that do not currently contain monograph ingredients will need to be reformulated. Manufacturers may reformulate to monograph ingredients without doing any clinical testing. In some cases, combination products will need to be reformulated to delete one or more ingredients. Such products can be reformulated to contain monograph ingredients at monograph concentrations and can remain in the marketplace with appropriate monograph labeling. If reformulation is necessary, the cost of doing so will vary among manufacturers based on the reformulation choice selected and the costs involved to do product specific stability testing and other standard manufacturing procedures. The agency believes that the majority of the OTC topical antifungal drug products currently marketed already contain monograph ingredients and, thus, will only need to be relabeled and not need to be reformulated. Therefore, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

The agency has determined under 21 CFR 25.24(c)(6) that this action is of a

type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

The agency is also removing § 310.201(a)(29) because the conditions in that section for tolnaftate are superseded by the requirements of this final monograph on OTC antifungal drug products (subpart C of 21 CFR part 333).

List of Subjects

21 CFR Part 310

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

21 CFR Part 333

Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 310 and 333 are amended 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, 721 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, 379e); 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) and reserving it.

3. Section 310.545 is amended by adding new paragraph (a)(22)(iv), by revising paragraph (d) introductory text, and by adding new paragraph (d)(15) to read as follows:

§ 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.

(a) * * *

(22) * * *

(iv) *Ingredients.*

Camphorated metacresol
Chloroxylenol
m-cresol
Nystatin

* * * * *

(d) Any OTC drug product that is not in compliance with this section is subject to regulatory action if initially introduced or initially delivered for introduction into interstate commerce after the dates specified in paragraphs (d)(1) through (d)(15) of this section.

* * * * *

(15) September 23, 1994, for products subject to paragraph (a)(22)(iv) of this section.

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

4. 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).

5. New subpart C, consisting of §§ 333.201 through 333.280, is added 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) Reference 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 certain 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 infection caused by certain dermatophytic fungi; 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 certain dermatophytic fungi.

§ 333.210 Antifungal active ingredients.

The active ingredient of the product consists of any one of the following within the specified concentration established for each ingredient:

(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 that 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," the phrase listed in paragraph (b)(1)(i) of this section and may contain the additional phrase listed in paragraph (b)(1)(ii) of this section. Other truthful and nonmisleading statements, describing only the indications for use that have been established in paragraph (b) of this section, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (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 identified in § 333.210 labeled for the treatment of athlete's foot, jock itch, and ringworm.* (i) (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:

(A) "Athlete's foot," athlete's foot (dermatophytosis)," "athlete's foot (tinea pedis)," or "tinea pedis (athlete's foot)";

(B) "Jock itch," "jock itch (tinea cruris)," or "tinea cruris (jock itch)"; or

(C) "Ringworm," "ringworm (tinea corporis)," or "tinea corporis (ringworm)."

(ii) In addition to the information identified in paragraph (b)(1)(i) of this section, the labeling of the product may contain the following statement: (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").

(2) *For products containing the ingredient identified in § 333.210(e) labeled for the prevention of athlete's foot.* (i) (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."

(ii) In addition to the information identified in paragraph (b)(2)(i) of this section, the labeling of the product may contain the following statement: "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 § 330.210.* (i) "Do not use on children under 2 years of age unless directed by 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 boldface 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.* [Select one of the following: "Clean" or "Wash"] "the affected area and dry thoroughly. Apply" (the word "spray" may be used to replace the word "apply" for aerosol products) "a thin layer of the product over affected area twice daily (morning and night) or as directed by a doctor. Supervise children in the use of this product. For athlete's foot: Pay special attention to spaces between the toes; wear well-fitting, ventilated shoes, and change shoes and socks at least once daily. For athlete's foot and ringworm, use daily for 4 weeks; for jock itch, use daily for 2 weeks. If condition persists longer, consult a doctor. 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 athlete's foot," (select one of the following: "clean" or "wash") "the feet and dry thoroughly. Apply" (the word "spray" may be used to replace the word "apply" for aerosol products) "a thin layer of the product to the feet once or twice daily (morning and/or night). Supervise children in the use of this product. Pay special attention to spaces between the toes; wear well-fitting, ventilated shoes, and 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.

§ 333.230 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: September 17, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

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