**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**21 CFR Part 333**

**[Docket No. 80N-476D]**

**RIN 0905-AA06**

## Topical Antifungal Drug Products for Over-the-Counter Human Use; Proposed Rulemaking for Diaper Rash Drug Products

**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 amending the notice of proposed rulemaking for over-the-counter (OTC) topical antifungal drug products. (See the **Federal Register** of December 12, 1989; 54 FR 51136). This part of the proposed rulemaking concerns conditions under which OTC topical antifungal drug products for the treatment or prevention of diaper rash are not generally recognized as safe and effective, and are misbranded. FDA is issuing this notice of proposed rulemaking after considering the statement on OTC drug products for the treatment of diaper rash of the Advisory Review Panel on OTC Miscellaneous External Drug Products and public comments on an advance notice of proposed rulemaking that was based on that statement. The agency's proposals concerning the use of other OTC diaper rash drug products are being published elsewhere in this issue of the **Federal Register**. These proposals are part of the ongoing review of OTC drug products conducted by FDA.

**DATES:** Written comments, objections, or requests for oral hearing on the proposed rulemaking before the Commissioner of Food and Drugs by December 17, 1990. The agency is allowing a period of 180 days for comments and objections instead of the normal 60 days for the following reasons: (1) The concurrent publication of four rulemakings regarding OTC diaper rash drug products and (2) this document contains the agency's initial evaluation of the submissions of data on OTC diaper rash drug products that were made to, but not reviewed by, the Advisory Review Panel on OTC Miscellaneous External Drug Products (Miscellaneous External Panel). New data by June 20, 1991. Comments on the new data by August 20, 1991. Written comments on the agency's economic impact determination by December 17, 1990.

**ADDRESSES:** Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 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 September 7, 1982, FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), advance notices of proposed rulemaking and reopened the administrative records for OTC topical antifungal drug products (47 FR 39464), topical antimicrobial drug products (47 FR 39406), external analgesic drug products (47 FR 39412), and skin protectant drug products (47 FR 39436) to allow for consideration of a statement on OTC drug products for the treatment of diaper rash prepared by the Miscellaneous External Panel, which was the advisory review panel responsible for evaluating data on the active ingredients used for the treatment of diaper rash. Interested persons were invited to submit comments by December 6, 1982. Reply comments in response to comments filed in the initial comment period could be submitted by January 5, 1983.

In the **Federal Register** of December 28, 1982 (47 FR 57738), in response to a request for an extension of time, the comment period and reply comment period for OTC topical antifungal drug products were extended to February 4, 1983, and to March 7, 1983, respectively.

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 (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information.

Two drug manufacturers, one trade association, and one manufacturer of diapers submitted comments. Most of these comments are general in scope and were submitted to more than one of the four rulemakings mentioned above. All of the overlapping comments were submitted to the rulemaking for OTC skin protectant drug products. In those cases where the same comments were submitted to more than one rulemaking, the comments are being addressed only once—in the notice of proposed rulemaking to amend the notice of proposed rulemaking for OTC skin protectant drug products. Copies of the comments received are on public display in the Dockets Management Branch.

The Panel provided a general statement on OTC drug products for the treatment of diaper rash, but did not review individual ingredients nor develop labeling for diaper rash drug products. The agency is aware that a number of diaper rash drug products are labeled for both the treatment and prevention of diaper rash. Therefore, the agency is expanding the scope of this rulemaking to include drug products labeled for both or either use.

In this notice of proposed rulemaking, FDA responds to public comment and states for the first time its position on OTC topical antifungal drug products for the treatment or prevention of diaper rash. Final agency action on this matter will occur with the publication at a future date of a final rule relating to OTC topical antifungal drug products for use in diaper rash. Other documents concerning the use of OTC topical antimicrobial drug products, OTC external analgesic drug products, and OTC skin protectant drug products for the treatment or prevention of diaper rash are being published separately, elsewhere in this issue of the **Federal Register**. This proposal constitutes FDA's tentative adoption of the Panel's statement on OTC topical antifungal drug products for use in diaper rash as modified on the basis of the comments received and the agency's independent evaluation of the Panel's statement.

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.

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 notices published in the Federal Register of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179) or to additional information that has come to the agency's attention since publication of the advance notices 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

The agency has reviewed the comments submitted to this rulemaking and, as noted above, determined that most of the comments were submitted to more than one of the four rulemakings related to OTC diaper rash drug products. The majority of the comments are general in scope or deal primarily with the use of skin protectant active ingredients. The agency has decided to address all of these general comments in a single rulemaking, which is the notice of proposed rulemaking to amend the tentative final monograph for OTC skin protectant drug products, published elsewhere in this issue of the Federal Register. These comments are incorporated into this rulemaking.

Regarding those portions of the comments that concerned topical antifungal active ingredients, one comment stated that secondary infections caused by bacteria and fungus may accompany diaper rash as complications; however, unlike common diaper rash, such secondary infections should be diagnosed and treated by a physician.

The agency agrees with the comment that complications of common diaper rash should be diagnosed and treated by a physician. Fungal and bacterial infections are the most common complications of diaper rash and usually result from a lack of treatment or improper treatment of the initial condition. The moist, warm, alkaline environment created by unchanged diapers is conducive to the proliferation of many bacteria and fungi which, in this environment, can cause secondary infections. Because the clinical picture is often obscure, the only precise method of determining the cause of the secondary infection is by laboratory analysis of scrapings from the affected area (Ref. 1). Therefore, a physician should be consulted for a definitive diagnosis followed by appropriate treatment of complications of diaper rash.

As stated in Part III. below—The Agency's Tentative Conclusions and Adoption of the Panel's Statement, the agency has determined that topical antifungal active ingredients should not be included in OTC diaper rash drug products because a fungus infection associated with diaper rash in infants and young children (the target population for these products) would not be amenable to proper diagnosis and treatment without the aid of a physician.

Reference

(1) Smith, G.H., "Diaper Rash and Prickly Heat Products," *in* "Handbook of Nonprescription Drugs," 8th Ed., American Pharmaceutical Association, Washington, p. 644, 1986.

## II. The Agency's Evaluation of the Submissions

Of the ingredients listed in the Panel's statement, the following are currently included in the rulemaking for OTC topical antifungal drug products: benzethonium chloride, boric acid, calcium undecylenate, camphor, chloroxylenol, 8-hydroxyquinoline, menthol, phenol, resorcinol, and salicylic acid. The agency has reviewed the submissions to the Panel and determined that only one submission was for a product containing any of these ingredients with labeling claims for antifungal activity for use in the treatment of diaper rash (Ref. 1). Another submission (Ref. 2) was for a diaper rash product with antifungal claims containing the ingredient sodium propionate, which was not listed in the Panel's statement, but was included in the rulemaking for OTC topical antifungal drug products.

The first submission was for two products (an ointment and a powder) for which the manufacturer's labeling listed the antifungal, calcium undecylenate, as the active ingredient (Ref. 1). Other information in the submission indicated that boric acid was also an active ingredient in the powder product. Both products were promoted for diaper rash, prickly heat, chafing, and minor skin irritations. Calcium undecylenate is discussed for its antifungal claims in this proposal and for its antibacterial claims in the proposal for OTC topical antimicrobial diaper rash drug products published elsewhere in this issue of the Federal Register.

The submission on the products containing 15 percent calcium undecylenate (ointment) and 15 percent calcium undecylenate and 3 percent boric acid (powder) did not include any studies on the ointment. Summaries of clinical studies and related case histories described the use of a powder product containing 5-percent boric acid and 15 percent calcium undecylenate on infants with diaper dermatitis and reported that successful therapeutic results were obtained in most cases. One large-scale clinical investigation (Ref. 3) reported a 12.5-percent incidence of rashes in 168 babies who had clear skin at the start of the study and who were treated with a powder containing 5 percent boric acid and 15 percent calcium undecylenate compared to a 21 percent incidence of rashes in 114 babies who were treated with a powder containing 5 percent boric acid but no calcium undecylenate. No evidence of skin irritation attributable to the boric acid/calcium undecylenate powder was observed in studies where infants received the powder as treatment for diaper rash or when it was used prophylactically. However, none of these studies provide sufficient data on the use of a lower concentration of calcium undecylenate alone to establish the safety and efficacy of the ingredient.

Since the time of the original submission, both products have been reformulated (Ref. 4). The powder product now contains 10 percent calcium undecylenate as the sole active ingredient, and the ointment product contains 53.9 percent petrolatum and 15 percent zinc oxide as the active ingredients,

Additional studies, both published and unpublished, have been submitted (Ref. 4) to demonstrate the antibacterial and antifungal activity of undecylenic acid and its salts for use on diaper rash. In in vitro studies using 5, 10, and 15 percent calcium undecylenate, significant zones of inhibition of *Candida albicans* (*C. albicans*) were demonstrated. One additional in vivo study involving 200 infants with varying degrees of diaper rash was submitted. One hundred of the infants were treated with a 15-percent calcium undecylenate/3-percent boric acid product and the remaining infants were treated with cornstarch or a bland baby powder and served as the control group. Cultures were taken and examined from all the infants. Of the six cases with *C. albicans* treated with the powder product, improvement was reportedly excellent in two cases and moderate in four cases. No data were provided on the control group. The agency concludes that the submitted studies are not adequately controlled and involve such a variety of concentrations of the undecylenate active ingredient, often with the active ingredient boric acid as well, that the effectiveness of 10 percent calcium undecylenate as the sole active ingredient has not been demonstrated and that additional studies are needed. There also remains a safety concern regarding use of any antifungal ingredient on infants. Undecylenic acid and its salts were recommended as Category I ingredients for use in the treatment of athlete's foot, jock itch, and ringworm by the Advisory Review Panel on OTC Antimicrobial (II) Drug Products. (See the **Federal Register** of March 23, 1982; 47 FR 12480.) The Panel required the following warning for all OTC topical antifungal drug products: "Do not use on children under 2 years of age except under the advice and supervision of a doctor."

The agency concurred with the Panel's Category I classification of undecylenic acid and its salts as well as the Panel's recommended warning for these products in the tentative final monograph for OTC topical antifungal drug products published in the **Federal Register** of December 12, 1989 (54 FR 51136 at 51146).

The second submission (Ref. 2) involves a product containing 5 percent sodium propionate and 0.0125 percent water-soluble derivatives of chlorophyll, labeled as a fungistatic, emollient ointment with a number of indications for use, including diaper rash. The company provided the information that the concentration of water-soluble chlorophyllin in the product was determined on the basis of that amount which proved necessary to effectively deodorize the propionate content and thereby make the preparation acceptable to patients. The submission cites a number of studies and review articles which report the safe and effective use of this product for a variety of dermatological conditions including diaper rash. However, none of these studies is a well-controlled clinical test.

The Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products recommended calcium and sodium propionate as Category I active ingredients for the relief of minor irritations of the vagina, based on clinical data on a product that has been marketed for 30 years as a prescription item. (See 48 FR 46694 at 46704; October 13, 1983.) The Panel also recommended the professional labeling claim "For the treatment of *Candida albicans*" for the propionates. The agency dissented from both of the Panel's recommendations because the data on the prescription product were reviewed under the Drug Efficacy Study Implementation (DESI) program, and it was found that the drug lacks substantial evidence of effectiveness (46 FR 46695). Accordingly, the agency placed the professional labeling indication recommended by the Panel in Category II and is not allowing OTC marketing of calcium or sodium propionate products for vaginal use.

The Advisory Review Panel on OTC Antimicrobial (II) Drug Products reviewed propionic acid and its salts for use in the treatment of athlete's foot, jock itch, and ringworm and found that these ingredients are safe, but that there are insufficient data available to permit final classification of their effectiveness. (See 47 FR 12480 at 12541; March 23, 1982.) With regard to the Category I classification for safety, the Panel recommended that all OTC antifungal drug products bear the label warning "Do not use in children under 2 years of age except under the advice and supervision of a doctor." The agency concurred with the Panel's recommendations in the tentative final monograph for OTC antifungal drug products (54 FR 51136 at 51161).

The agency tentatively concludes that neither the safety nor effectiveness of the propionates for use on infants has been adequately demonstrated, and that additional data are needed to support Category I status for use of any of the propionates in the treatment or prevention of diaper rash.

**References**

(1) OTC Volume 160236.

(2) OTC Volume 160105.

(3) Vignec, A.J., "Report on Prophylactic and Therapeutic Use of Desenex Baby Powder for a Three-Month Period Ending November 1," in OTC Volume 160236, pp. 83–116.

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

### III. The Agency's Tentative Conclusions and Adoption of the Panel's Statement

Although the Panel discussed the use of topical antifungal ingredients for the treatment of diaper rash, it did not review or classify any individual ingredients. All ingredients in marketed products submitted to the Panel or ingredients that appeared in the call-for-data notices were simply listed in the Panel's statement on OTC topical antifungal drug products for the treatment of diaper rash (47 FR 39464). The Panel recommended that the use of topical antifungal ingredients included in this list be referred to the rulemaking for OTC topical antifungal drug products and requested comments from any interested person on the use of any of these ingredients for the treatment of diaper rash. The Panel did note that common diaper rash is often accompanied by a secondary infection of *C. albicans*, which is frequently present in feces and proliferates under the diaper to produce a characteristic bright red, sharply marginated rash with satellite pustules and erosions. The Panel also pointed out that physicians treat severe diaper rash with topical antifungal and anticandidal drugs, often in combination with a topical steroid (47 FR 39467).

As discussed above, only one of the comments addressed the use of topical antifungal active ingredients in diaper rash drug products. The agency agrees with the comment that fungus infections associated with diaper rash are not suitable for self-treatment by consumers and should be diagnosed and treated by a physician. This position is also supported by the Panel's comments about the type of treatment used when diaper rash is complicated by fungus (47 FR 39467). Other authors also agree with the Panel. For example, Schanzer and Wilkin (Ref. 2) and Honig (Ref. 3) state that only simple diaper rash should be treated with OTC drugs, and, if the rash has not healed in a reasonable amount of time, a secondary infection may be present (Refs. 1 and 2). Numerous authors point out that diaper dermatitis includes diverse disorders which appear in the diaper area, and identifying the etiology of a diaper rash and selecting the therapeutic agent are difficult even for a physician (Refs. 2 through 6). Schanzer and Wilkin (Ref. 2) noted that the diagnostic range includes irritant

dermatitis, allergic dermatitis, intertrigo, seborrheic dermatitis, atopic eczema, candidiasis, psoriasis, scabies, miliaria, bullous impetigo, and granuloma gluteale infantum. These authors developed a full page flow chart for the decisional process of diagnosing and treating diaper dermatitis to be used by family physicians before they refer a patient to a dermatologist.

The agency agrees with these experts that laypersons do not have adequate medical background or training to diagnose and treat such infections or other conditions in the diaper area. The agency believes that a physician should be consulted for diagnosis and appropriate therapy for the different types of diaper dermatitis described above, including fungal infection. In addition, as discussed below, topical antifungal drugs actually "treat" the underlying disease rather than merely alleviate symptoms. Accordingly, the agency believes it is appropriate that these drugs be used for diaper rash only under the supervision of a physician.

In the tentative final monograph for OTC topical antifungal drug products, the agency stated that topical antifungal drugs are different from most OTC drug products in that they actually treat the underlying disease rather than only ameliorate signs and symptoms (54 FR 51136 at 51154). The agency also proposed a label warning that these ingredients should not be used on children under 2 years of age except as recommended by a physician (54 FR 51161). In an adult, the surface area of contact is small (probably less than 5 percent) when antifungals are used for the approved OTC indications, i.e., athlete's foot, jock itch, and ringworm. In infants, the affected area of diaper rash may be 10 to 15 percent of the body surface. Additionally, inflamed and often open surface areas are more permeable than normal skin and permit a greater degree of absorption especially under occlusion as with a diaper. For these reasons, the agency does not believe that topical antifungal active ingredients should be used in OTC diaper rash drug products.

The presence of *C. albicans* in simple diaper rash is not clearly defined. Brookes, Hubbert, and Sarkany (Ref. 7) studied 60 infants on their regular well-baby visits to a family health clinic to determine the incidence of diaper rash and to clinically evaluate early cases. Cultures were taken from the skin of the normal group and the diaper rash group. *C. albicans* was recovered in only two of the infants with diaper rash (8 percent) and in none of the normal infants. The authors noted that *C. albicans* had a much higher incidence in other studies that included infants with long established and treated cases of diaper rash. The authors added that they had included in their study only infants in which diaper rash was an incidental finding and concluded that *C. albicans* plays no etiological role in early cases of diaper rash.

Pittillo et al. (Ref. 8) studied the microbial skin flora of the diaper area of 10 infants without a recent history of diaper dermatitis and 10 infants affected with diaper dermatitis. *C. albicans* was not recovered from the diaper area cultures of either test group.

In a study by Brown, Tyson, and Wilson (Ref. 9), six children in the control group had previously been studied while they had diaper rash; *C. albicans* was isolated from one child. This organism was not isolated following recovery.

Montes et al. (Ref. 10) obtained bacterial and fungal cultures from the diaper area of 35 infants with diaper dermatitis and from 25 normal controls. The infants with diaper rash were treated by their pediatricians by means of usual (unspecified) topical measures, and then 25 of the infants were recultured after cure of the dermatitis and while the infants were still wearing diapers. The after-cure infants were not sampled for at least 2 months to provide enough time to allow recolonization of the diaper area by the normal microbial flora. It was apparent that the presence of *C. albicans* differed in the after-cure group and the normal group compared to the diaper rash group. *C. albicans* was recovered from 77.1 percent of the infants with diaper rash, 8 percent of the after-cure infants, and 12 percent of the normal control infants. Because the treatments used on the infants were not described, it cannot be determined whether the changes in the microbial flora were due to the use of topical antimicrobial drugs or due to other conditions as the diaper rash cleared.

Based on the above studies, the agency believes that there is a lack of adequate data to determine if OTC topical antifungal active ingredients are needed for the treatment or prevention of simple diaper rash. Accordingly, based on all information available to date, the agency is proposing that any OTC topical antifungal drug product labeled for the treatment and/or prevention of diaper rash is not generally recognized as safe and effective. If this proposal is ultimately adopted, all OTC drug products labeled for the treatment and/or prevention of diaper rash would need to be formulated to contain no topical antifungal ingredients. Upon the effective date of that portion of the final rule for OTC topical antifungal drug products that applies to OTC diaper rash drug products, any OTC drug products containing topical antifungal active ingredients and labeled for the treatment and/or prevention of diaper rash that are initially introduced or initially delivered for introduction into interstate commerce would be regarded as unapproved new drugs and subject to regulatory action. Manufacturers are encouraged to comply voluntarily with the proposed rule at the earliest possible date.

**References**

(1) Smith, G.H., "Diaper Rash and Prickly Heat Products," *in* "Handbook of Nonprescription Drugs," 8th Ed., American Pharmaceutical Association, Washington, pp. 643–653, 1986.

(2) Schanzer, M.C., and J.K. Wilkin, "Diaper Dermatitis," *American Family Physician*, 25:127–132, 1982.

(3) Honig, P.J., "Diaper Dermatitis: Factors to Consider in Diagnosis and Treatment," *Postgraduate Medicine*, 74:79–88, 1983.

(4) Williams, M.L.K., "How I Treat Diaper Rashes," *Medical Times*, 108:50–53, 1980.

(5) Leyden, J.J., "Diaper Dermatitis," *Dermatologic Clinics*, 4:23–28, 1986.

(6) Weston, W.L., A.T. Lane, and J.A. Weston, "Diaper Dermatitis: Current Concepts," *Pediatrics*, 66:532–536, 1980.

(7) Brookes, D.B., R.M. Hubbert, and I. Sarkany, "Skin Flora of Infants with Napkin Rash," *The British Journal of Dermatology*, 85:250–253, 1971.

(8) Pittillo, R.F., et al., "Bacterial Flora of Infants' Skin: Comparison Between Diaper-Occluded and Unoccluded Areas," *International Journal of Dermatology*, 12:245–249, 1973.

(9) Brown, C.P., R.M. Tyson, and F.H. Wilson, "Dermatitis (Diaper Rash): A Bacteriologic Study of the Diaper Region," *The Pennsylvania Medical Journal*, 55:755–758, 1952.

(10) Montes, L.F., et al., "Microbial Flora of Infant's Skin: Comparison of Types of Microorganisms Between Normal Skin and Diaper Dermatitis," *Archives of Dermatology*, 103:400–406, 1971.

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 topical antifungal drug products for the treatment or prevention of diaper rash, 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 for the treatment or prevention of diaper rash 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 invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC topical antifungal drug products for the treatment or prevention of diaper rash. Types of impact may include, but are not limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC topical antifungal drug products for the treatment or prevention of diaper rash should be accompanied by appropriate documentation. Because the agency has not previously invited specific comment on the economic impact of the OTC drug review on topical antifungal drug products for the treatment or prevention of diaper rash, a period of 180 days from the date of publication of this proposed rulemaking in the **Federal Register** will be provided for comments on this subject to be developed and submitted. 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 invited public comment in the advance notice of proposed rulemaking regarding any impact that this rulemaking would have on OTC topical antifungal drug products used for the treatment of diaper rash. 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 December 17, 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 determined under 21 CFR 25.24(c)(6) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Interested persons may, on or before December 17, 1990, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed rulemaking. 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 December 17, 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 am. and 4 pm., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register.**

Interested persons, on or before June 20, 1991, 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 August 20, 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 (HFA–305) (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 for OTC topical antifungal drug products, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on August 20, 1990. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph for OTC topical antifungal drug products is published in the **Federal Register**, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Dated: April 24, 1999.

**James S. Benson,**

*Acting Commissioner of Food and Drugs.*

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