notice number of this NPRM. Persons interested in being placed on a mailing list for future NPRMs should also request a copy of Advisory Circular No. 11–2A, which describes the application procedure.

The Proposal

The FAA is considering an amendment to Part 71 of the Federal Aviaiton Regulations (14 CFR part 71) to establish Class E airspace area at Couldersport, PA. An RNAV Approach, Helicopter RNAV 343, has been developed for Charles Cole Memorial Hospital Heliport, Couldersport, PA. Controlled airspace extending upward from 700 feet AGL is needed to accommodate the SIAP. Class E airspace designations for airspace areas extending upward from 700 feet from or above the surface are published in Paragraph 6005 of FAA Order 7400.9H, dated September 1, 2000, and effective September 16, 2000, which is incorporated by reference in 14 CFR 71.1. The Class E airspace designation listed in this document would be published subsequently in the Order.

The FAA has determined that this proposed regulation only involves an established body of technical regulations for which frequent and routine amendments are necessary to keep them operationally current. Therefore, this proposed regulation—(1) is not a ''significant regulatory action'' under Executive Order 12866; (2) is not a ''significant rule'' under DOT Regulatory Policies and Procedures (44 FR 11034; February 26, 1979); and (3) does not warrant preparation of a regulatory evaluation as the anticipated impact is so minimal. Since this is a routine matter that would only affect air traffic procedures and air navigation, it is certified that this proposed rule would not have significant economic impact on a substantial number of small entities under the criteria of the Regulatory Flexibility Act.

List of Subjects in 14 CFR Part 71

Airspace, Incorporation by reference, Navigation (air).

The Proposed Amendment

In consideration of the foregoing, the Federal Aviation Administration proposes to amend 14 CFR part 71 as follows:

PART 71—[AMENDED]

1. The authority citation for 14 CFR part 71 continues to read as follows:

Authority: 49 U.S.C. 106(g), 40103, 40113, 40120; E.O. 10854, 24 FR 9565, 3 CFR , 1959–1963 Comp., p. 389.

§ 71.1 [Amended]

2. The incorporation by reference in 14 CFR 71.1 of Federal Aviation Administration Order 7400.9H dated September 1, 2000, and effective September 16, 2000, is proposed to be amended as follows:

Paragraph 6005 Class E airspace areas extending upward from 700 feet or more above the surface of the earth.

* * * * *

AEA PA E5 Couldersport, PA (New)

Charles Cole Memorial Hospital Heliport
Lat. 41°46′16.14″ N/long. 77°58′28″ W)

That airspace extending upward from 700 feet above the surface within a 6 mile radius of the Charles Cole Memorial Hospital Heliport.

* * * * *

Issued in Jamaica, New York, on May 15, 2001.

F.D. Hatfield,

Manager, Air Traffic Division, Eastern Region.

[FR Doc. 01–13311 Filed 5–25–01; 8:45 am]

BILLING CODE 4910–13–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 333

[Docket No. 96P–0460]

RIN 0910–AA01

Topical Antifungal Drug Products for Over-the-Counter Human Use; Proposed Amendment of Final Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a proposed rule that would amend the final monograph for over-the-counter (OTC) topical antifungal drug products to add the ingredient clotrimazole as generally recognized as safe and effective for the treatment of athlete's foot, jock itch, and ringworm. This proposal is part of FDA's ongoing review of OTC drug products.

DATES: Submit written comments by August 27, 2001. Submit written comments on the agency's economic impact determination by August 27, 2001. See section IX of this document for the effective date of any final rule that may publish based on this proposal.

ADDRESSES: Submit written comments to the Docket Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Gerald M. Rachanow, Center for Drug Evaluation and Research (HFD–560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2307.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of September 23, 1993 (58 FR 49890), FDA published a final monograph for OTC topical antifungal drug products in part 333 (21 CFR part 333), subpart C. That monograph includes six antifungal active ingredients used for the treatment of athlete's foot, jock itch, and ringworm and one ingredient used for the prevention of athlete's foot. The monograph provides that two ingredients may contain professional labeling (may be provided to health professionals but not to the general public) for the treatment of superficial infections caused by yeast (*Candida albicans*). A manufacturer submitted a citizen petition (Refs. 1 through 4) to include the antifungal ingredient clotrimazole in the monograph for both the OTC and professional labeling treatment claims. Subsequently, the manufacturer withdrew its request to include clotrimazole in the monograph for the professional labeling treatment claim (Ref. 5).

II. The Agency's Evaluation of the Citizen Petition

A. General Background

Clotrimazole is a member of the imidazole class of antifungal drugs and is recognized in the U.S. Pharmacopeia (Ref. 6). Clotrimazole has been marketed as a topical antifungal at a 1-percent concentration in the United States as a prescription product since 1975 and as an OTC product since 1989 under new drug applications (NDAs) in cream, lotion, and solution dosage forms. The agency notes that clotrimazole has also been marketed OTC in a number of other countries, the first marketing occurring in 1980. Distribution figures (Ref. 1) indicate a significant amount of the drug has been marketed OTC in the United States and other countries since 1990. Miconazole nitrate, a related member of the imidazole class of antifungal drugs, is currently included as an active ingredient in § 333.210(c) of the final monograph for OTC topical antifungal drug products.

B. Safety

The toxicity of clotrimazole has been well-studied (Refs. 1 and 2). Acute

toxicity has been studied in a variety of animal species. When administered intraperitoneally, the LD50 was approximately 500 milligrams/kilogram (mg/kg) for mice and 1,200 mg/kg for rats. Subacute dermal toxicity studies in rabbits (comparing clotrimazole cream or solution to its vehicle) did not reveal any significant dermal or systemic changes. Other dermal tolerance studies showed minimal irritation from clotrimazole, and they showed that skin reactions on rabbits were essentially the same for the drug and the vehicle cream, solution, or lotion. Ocular tolerance studies in rabbits showed slight conjunctival reddening and mild irritation for both clotrimazole cream or solution and its vehicle, which subsided 48 to 72 hours after instillation.

Studies have shown clotrimazole is very poorly absorbed following dermal application. Duhm et al. (Ref. 7) reported that topical administration of radiolabeled 1-percent clotrimazole cream or solution to normal skin resulted in less than 0.5 percent of the activity excreted in the urine up to 5 days after application of the cream and less than 0.05 percent up to 4 days after application of the solution. When the solution was applied to acutely inflamed skin, 0.15 percent of the activity was excreted in the urine. This amount was slightly higher than after applying the solution to normal skin. In all subjects, urinary excretion was largely completed 2 to 3 days after application. No definitely measurable amounts of radioactivity were found in the serum of any of the subjects in whom the radiolabeled clotrimazole cream or solution was applied to intact or inflamed skin until 48 hours after application. The equivalent clotrimazole concentrations were below the detection limit of 0.001 microgram of clotrimazole per milliliter (mL) of serum.

Reproduction studies in animals showed, in general, that clotrimazole was well tolerated and had no teratogenic effect. All reproduction studies (Ref. 1) were done with oral dosing, 25 to 200 mg/kg in mice and rats and 60 to 180 mg/kg in rabbits. The only adverse effects noted were: (1) Lower fetal weights and more resorptions in rats given 100 mg/kg, and (2) clotrimazole at 200 mg/kg was lethal to pregnant rats. Mutagenic studies in Chinese hamsters showed that clotrimazole had no mutagenic effect. An 18-month oral dosing study of clotrimazole in rats did not show any carcinogenic effect.

Clotrimazole has an excellent safety record during its 24-year history of marketing as a prescription and OTC topical antifungal drug in the United States. The manufacturer has reported 555 adverse drug events (ADEs) from March 1975 through March 1996. Of these, 240 (43 percent) are reports of ''therapeutic response decrease'' (lack of effectiveness) with topical antifungal treatment. The majority of the ADEs were topical and nonserious in nature. Pruritis (itching), rashes, erythema (abnormal redness of the skin), and paresthesia (abnormal sensation of the skin, such as burning, stinging, or tingling) were the most common events reported and are common to all topical antifungal drugs. Rarely, individuals experienced a systemic allergic reaction. The number and nature of reported ADEs is similar before and after clotrimazole OTC marketing in the United States began in 1989.

The contact sensitization potential of 1-percent clotrimazole cream was determined using the Maximization Test (26 subjects) and the Draize Repeat Insult Test (207 subjects) (Ref. 2). No sensitization occurred in either test. There are no known drug interactions, abuse potential, or overdose potential associated with clotrimazole when applied topically to the skin for antifungal use. There have been infrequent reports of consumers mistaking the solution (10 mL container) product for eye drops and instilling it in their eyes. All eye effects reported have been minor and transient and were completely relieved by flushing the eye with water or the passing of a short period of time. Although these effects have been minor, § 333.250(c)(1)(iii) of the monograph for OTC topical antifungal drug products includes the warning: ''Avoid contact with the eyes.''

C. Effectiveness

Clotrimazole has been shown in a number of controlled studies to be an effective OTC topical treatment for tinea pedis (athlete's foot), tinea cruris (jock itch), and tinea corporis (ringworm). The causative organisms in these studies were primarily the same organisms for which clotrimazole is indicated: *Trichophyton rubrum* (*T. rubrum*), *Trichophyton mentagrophytes* (*T. mentagrophytes*), and *Epidermophyton floccosum* (*E. floccosum*).

Knox, Zaias, and Battistini (Refs. 2 and 3, Delbay 004) compared the antifungal effectiveness of 1-percent topical clotrimazole with its vehicle in 71 subjects (61 subsequently acceptable for efficacy evaluation) who had ringworm (16), jock itch (15), ringworm and jock itch (7), and athlete's foot (23). The fungus infections were mycologically confirmed by KOH (potassium hydroxide) preparation and/or culture. Subjects applied the assigned products (double-blind, randomized, parallel study) twice a day for 28 days and were evaluated clinically weekly for 5 weeks, with samples taken each week for KOH preparation and culture. Of the 61 cases (27 on active and 34 on vehicle) evaluated, mycological conversion rates (a change from positive to negative of both KOH preparation and culture) for tinea corporis/cruris were 76 percent (13/17) for active and 5 percent (1/21) for vehicle ($P<0.001$) and for tinea pedis 60 percent (6/10) for active and 0 (0/13) for vehicle ($P=0.002$). The fungus most frequently detected was *T. rubrum*. Eight of 12 subjects (67 percent) in the clotrimazole group who had severe clinical signs and symptoms were clinically cured compared to 0 of 14 in the vehicle group ($P=0.0003$).

Clayton and Connor (Refs. 2, 3, 4, and 8, Delbay 007) compared 1-percent clotrimazole cream (50 subjects) to Whitfield's Ointment (3-percent salicylic acid and 6-percent benzoic acid) (52 subjects) and to nystatin ointment (14 subjects) in treating several fungal infections in a randomized, double-blind trial based on the subject's condition. Subjects with mycologically positive skin infection (by culture and/or microscopy of skin scrapings) were assigned to a test medication depending on their diagnosis. The nystatin ointment arm of the study did not include any subjects with tinea infections and, thus, is not discussed further. Subjects with a fungal infection applied clotrimazole cream or Whitfield's Ointment twice daily for 28 days. Followup examinations were conducted at 2, 4, and 8 weeks for most subjects. There were 100 evaluations of subjects who had ringworm/jock itch and athlete's foot (some subjects had both) and who applied clotrimazole or Whitfield's Ointment. Mycological conversion rates for subjects with ringworm/jock itch were 65 percent (13/20) for clotrimazole and 63 percent (12/19) for Whitfield's Ointment ($P=1.00$), and for subjects with athlete's foot 63 percent (19/30) for clotrimazole and 58 percent (18/31) for Whitfield's Ointment ($P=0.795$). There were no statistically significant differences between the treatments, and the 1-percent clotrimazole cream was considered as effective as Whitfield's Ointment, the accepted treatment available at that time, for treating tinea infections. The investigators noted that there were a greater number of side effects, usually mild irritation or burning, with the Whitfield's Ointment (14 of 52 subjects) than with the clotrimazole cream. Some

subjects had no side effects, while others had more than one. The total of 116 represents side effects recorded for subjects at any visit.

Smith et al. (Refs. 2, 3, and 4, Delbay 003) compared the antifungal and clinical effectiveness of 1-percent clotrimazole topical solution against its vehicle (polyethylene glycol 400) in a randomized, double-blind study in 169 subjects, of which 131 were eventually evaluated. Thirty eight subjects were excluded from the study for various reasons, with almost half of these lost to followup. Fungal infections were confirmed by KOH preparation and/or culture; 120 subjects had fungal infections (11 had candidiasis). Subjects applied the test solutions twice daily for 28 days (65 used the active and 66 used the vehicle). Effectiveness was determined on the basis of mycological findings, clinical findings (severity of signs and symptoms), and overall assessment of the treatment. Mycological conversion rates for subjects with tinea corporis/cruris were 96 percent (27/28) for the active and 34 percent (10/29) for the vehicle (P<0.001). The conversion rates for subjects with tinea pedis were 39 percent (12/31) for the active and 25 percent (8/32) for the vehicle. Weekly sign and symptom severity was evaluated on a scale of 1 (= none) to 4 (= severe). The weekly average for clotrimazole subjects declined from 3.25 at week 0 to 1.82 at week 4, while placebo declined from 3.14 to 2.52 for the same times (P=0.009). The authors stated that the treatment results clearly demonstrated the mycological and clinical effectiveness of the 1-percent clotrimazole solution and that the product was tolerated very well. The agency has some concerns about the usefulness of the clinical data as a scale of weekly averages of signs and symptoms. This information does not enable a determination to be made whether the subjects were actually clinically cured or just clinically improved. While the data lack sufficient clinical meaning for the agency to consider this a primary supportive study, the agency considers this study partially supportive of tinea corporis/cruris claims, but not tinea pedis claims. Tinea pedis claims are supported by other studies discussed in this document.

Smith and Knox (Refs. 2 and 3, Delbay 005) used the clotrimazole solution to continue to treat 22 subjects from the previous study who failed to respond mycologically to the vehicle solution in an open, mycologically controlled study with no control group. The drug was applied twice a day for 2 to 6 weeks depending on the clinical response. Eight subjects' fungal infections cleared completely both mycologically and clinically; 4 became negative mycologically and improved clinically, but did not heal completely; and 10 improved clinically but had residual positive mycology. None of the subjects reported any adverse events due to the drug. The agency finds that this study lacked sufficient details to be useful to support effectiveness.

Eaglestein et al. (Refs. 2, 3, and 4, Delbay 008) compared the antifungal and clinical effectiveness of 1-percent clotrimazole topical solution to its vehicle in a study of 124 subjects with tinea corporis/cruris using essentially the same design as the Smith et al. study (Delbay 003). Of these, 36 were not included in the final evaluation (14 were lost to followup and 22 were treated for a longer or shorter period than the 4 weeks stipulated in the protocol). Of the 88 subjects who met all of the criteria for evaluation of effectiveness, 29 had ringworm, 51 had jock itch, and 8 had both conditions; 42 of these subjects used the active and 46 used the vehicle. After 28 days of treatment, the mycological conversion rates were 88 percent (37 of 42) for the active and 28 percent (13 of 46) for the vehicle (P<0.001). The primary fungus detected was *T. rubrum*. The clinical investigators evaluated overall severity of clinical signs and symptoms (e.g., scaling, itching, inflammation) and indicated that 40 of 41 clotrimazole subjects improved clinically, compared to 24 of 45 vehicle subjects (P<0.001). One subject in each group could not be evaluated in this regard because a pretreatment severity was not specified. The clinical investigators' assessment of the treatment was that 34 of 42 clotrimazole subjects were healed clinically compared to 7 of 46 vehicle subjects (P<0.001). The authors stated that the results indicated that 1-percent clotrimazole solution is very effective for topical treatment of ringworm, especially on smooth and bare skin. The agency finds this study supportive of a ringworm claim.

Eaglestein et al. (Refs. 2, 3, and 4, Delbay 008) compared the anitfungal and clinical effectiveness of 1-percent clotrimazole topical solution to its vehicle in a study of 124 subjects with tinea corporis/crutis using essentially the same design as the Smith et al. study (Delbay 003). Eaglestein et al. (Ref. 2, Delbay 011 and 012) compared the antifungal and clinical effectiveness of 1-percent clotrimazole topical solution to its vehicle in subjects with two nonvesicular types of tinea pedis: (1) Plantar hyperkeratosis (moccasin), and (2) interdigital and/or instep, using the same design as the Smith et al. study (Delbay 003). The mycological conversion rates for subjects with plantar hyperkeratosis were 76 percent (28 of 37) for the clotrimazole group and 39 percent (16 of 41) for the vehicle group (P=0.001) and for subjects with interdigital and/or instep were 66 percent (23 of 35) for the drug group and 39 percent (13 of 33) for the vehicle group (P=0.026). Thirty of 37 (80 percent) drug treated subjects with plantar hyperkeratosis improved clinically compared to 24 of 41 (59 percent) vehicle subjects (P=0.027), while 22 of 34 (65 percent) drug treated subjects with interdigital and/or instep improved clinically compared to 20 of 33 (61 percent) vehicle subjects (not statistically significant). While the fungi most frequently detected in the subjects were *T. rubrum* and *T. mentagrophytes*, organisms for which the drug is indicated for OTC use, the OTC product labeling does not include claims for plantar hyperkeratosis or interdigital and/or instep tinea pedis. Thus, these studies provide support but do not establish effectiveness for OTC use.

Fredriksson (Ref. 9) compared the antifungal and clinical effectiveness of 1-percent clotrimazole topical solution to its vehicle in a randomized, double-blind, parallel study in 54 subjects. Half of the subjects had tinea infections: Tinea pedis (17), tinea cruris (8), tinea corporis (1), and tinea capitis (1). *T. rubrum* was the fungus most frequently detected. The 27 subjects applied test products (17 used clotrimazole and 10 used placebo) twice daily for 21 days, at which time the study was decoded. The 10 vehicle-treated failures were then crossed-over to an open study with clotrimazole treatment for another 21 days. After 3 weeks of applying the 1-percent clotrimazole solution, all 27 subjects (both the initial active group and crossover vehicle failures) with tinea infections were mycologically cured, and 19 of the 27 subjects (70 percent) had no clinical evidence of disease. The agency considers this study supportive of effectiveness.

The Advisory Review Panel on OTC Antimicrobial (II) Drug Products (the Panel) discussed two studies involving clotrimazole (Refs. 10 and 11) in its evaluation of haloprogin (47 FR 12480 at 12493 and 12494, March 23, 1982). One double-blind, clinical study (Ref. 10) compared the effectiveness of 1-percent clotrimazole solution with 1-percent haloprogin solution (the topical antifungal drug product monograph concentration in § 333.210(b)). Based on the results of the study, the authors concluded that clotrimazole was

significantly more effective than haloprogin for jock itch. The other double-blind, randomized study (Ref. 11) compared 1-percent clotrimazole cream and solution and 1-percent haloprogin ointment and solution in the treatment of subjects with athlete's foot and ringworm of the body. The author concluded that there were no marked differences in the antifungal effectiveness of clotrimazole and haloprogin.

D. Response to Comment

One comment (Ref. 12), submitted in response to the citizen petition (Ref. 1), opposed monograph status for clotrimazole. The comment contended that safety, effectiveness, and therapeutic effect will not be assured through the OTC drug monograph process because neither bioequivalence nor formulation changes will be monitored by the agency. The comment argued that topical antifungal drug products present interesting formulation and manufacturing issues and that the agency could assure safety, effectiveness, and interchangeability of clotrimazole products only through its application preapproval process. The comment noted the Panel's discussion about vehicles for OTC topical antifungal drug products (47 FR 12480 at 12489 and 12490). The Panel discussed types and effects of different vehicles, vehicle solubility and viscosity, and the rate of diffusion of an antifungal drug from a vehicle.

The agency disagrees with the comment. The agency does not consider the inclusion of clotrimazole in the topical antifungal drug products monograph at this time as any different than the previous inclusion of the former new drugs haloprogin and miconazole nitrate in the monograph. Bioequivalence testing is not required for either of those drugs currently marketed under the monograph. Based on the previous monograph determinations for haloprogin and micinazole nitrate and the marketing of clotrimazole OTC under NDA's since 1989, the agency considers all three of these ingredients to have an extensive history of safe and effective OTC use. While formulation and manufacturing issues for topical products may prevent FDA from allowing monograph status, the agency has no evidence at this time to indicate that formulation and manufacturing issues have affected the safety and effectiveness of clotrimazole.

The Panel's discussion about vehicles for these products was based on the Panel's general knowledge. Data on specific vehicles were not submitted to or reviewed by the Panel. No comments were received on the Panel's discussion about vehicles for these products, and this issue did not arise further in the rulemaking in determining which antifungal ingredients could be included in the final monograph. The agency monitors the quality of all products marketed under OTC drug monographs through its current good manufacturing practice regulations in 21 CFR part 211 and its inspection authority. If clotrimazole is marketed under the final monograph, the agency will monitor the quality of clotrimazole products in the same manner as other products currently marketed under the monograph.

E. Labeling

Since 1989, antifungal drug products containing clotrimazole 1 percent have been marketed OTC in the United States with indications for the treatment of athlete's foot (tinea pedis), jock itch (tinea cruris), and ringworm (tinea corporis). The warnings and directions in the approved applications for these products are very similar to those contained in § 333.250(c) and (d) of the final monograph for OTC antifungal drug products. If a manufacturer chooses to market its clotrimazole product that is currently marketed OTC under an approved application under the monograph in the future, it will have to modify the product's labeling to conform to the OTC drug monograph labeling in § 333.250. In either case, the manufacturer will need to follow the new OTC drug content and format labeling requirements in § 201.66 (21 CFR 201.66).

III. The Agency's Tentative Conclusions and Proposals

The agency has determined that clotrimazole has been marketed to a material extent and for a material time as a topical antifungal drug and, based on the available data, can be generally recognized as safe and effective for this use and included in the OTC drug monograph for this class of products. Therefore, the agency is proposing to add clotrimazole 1 percent as new paragraph (g) in § 333.210.

The agency is allowing interim marketing of OTC topical antifungal drug products containing 1-percent clotrimazole with claims for the treatment of athlete's foot (tinea pedis), jock itch (tinea cruris), and ringworm (tinea corporis) to begin with the publication of this proposal to amend the monograph based on the OTC marketing experience in the United States since 1989 and because there are no labeling issues to be addressed at this time. Such interim marketing is subject to the risk that the agency may adopt a different position in the final rule that could require relabeling, recall, or other regulatory action. Any product containing clotrimazole that is marketed under the monograph before a final rule is issued must use all of the labeling that is required by the final monograph (part 333, subpart C) and must follow the content and format requirements in § 201.66.

This proposal does not apply to clotrimazole marketed OTC as an antifungal agent in intravaginal drug products labeled for the treatment of vaginal yeast infections. The existing monograph for topical antifungal drug products does not contain any claims for intravaginal use.

IV. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Comment No. CP1, Docket No. 96P–0460, Dockets Management Branch.
2. Comment No. SUP1, Docket No. 96P–0460, Dockets Management Branch.
3. Comment No. LET3, Docket No. 96P–0460, Dockets Management Branch.
4. Comment No. LET4, Docket No. 96P–0460, Dockets Management Branch.
5. Comment No. LET5, Docket No. 96P–0460, Dockets Management Branch.
6. *The United States Pharmacopeia 24–The National Formulary 19*, The United States Pharmacopeial Convention, Inc., Rockville, MD, p. 451, 1999.
7. Duhm, B. et al., ''Pharmacokinetics of Topically Applied Bisphenyl-(2-chlorophenyl) -1-imidazolyl-methane-[14C],'' *Arzneittelforschung*, 22:1289–191, 1972, English version, *Drugs Made in Germany*, 15:126–132, 1972.
8. Clayton, Y. M. and B. L. Connor, ''Comparison of Clotrimazole Cream, Whitfield's Ointment and Nystatin Ointment for the Topical Treatment of Ringworm Infections, Pityriasis Versicolor, Erythrasma, and Candidiasis,'' *British Journal of Dermatology*, 89:297–303, 1973.
9. Fredriksson, T., ''Topical Treatment with Bay b 5097, A New Broad Spectrum Antimycotic Agent,'' *British Journal of Dermatology*, 86:628–630, 1972.
10. Van Dersarl, J. V. and R. H. Sheppard, ''Clotrimazole vs. Haloprogin Treatment of Tinea Cruris,'' *Archives of Dermatology*, 113:1233–1235, 1977.
11. Weitgasser, H., ''Clinical and Mycologic Trials with the Antifungal Medication Haloprogin,'' *Mykosen*, 20:15–24, 1977.
12. Comment No. C1, Docket No. 96P–0460, Dockets Management Branch.

V. Analysis of Impacts

FDA has examined the impacts of this proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5

U.S.C. 601–612) (as amended by subtitle D of the Small Business and Regulatory Fairness Act of 1996 (Public Law 104–121)), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4) (2 U.S.C. 1501 *et seq.*). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act requires that agencies prepare a written statement and economic analysis before proposing any rule that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation).

The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the proposed rule is not a significant regulatory action as defined by the Executive Order, as explained below, and so is not subject to review under the Executive Order.

The purpose of this proposed rule is to include clotrimazole 1 percent in the monograph for OTC topical antifungal drug products. This proposal allows current manufacturers of these products to market their products under the OTC drug monograph instead of an NDA and enables other manufacturers who wish to market clotrimazole products OTC to enter the marketplace without having to obtain an NDA. In both cases, there will be cost savings from marketing without an NDA.

If current manufacturers of these products choose to market them under the OTC drug monograph, they should incur only minor costs to relabel their products to meet the monograph. Some manufacturers may have to add a warning that was included in the final monograph, but not required when some products containing clotrimazole were approved for OTC marketing under an NDA. These manufacturers can make this change whenever they are ready to order new product labeling. Manufacturers have informed the agency that this type of relabeling cost generally averages about $2,000 to $3,000 per stock keeping unit (SKU) (individual products, packages, and sizes). Based on information in the agency's Drug Listing System, there are less than 10 manufacturers and distributors that together produce about 25 SKU's of OTC topical antifungal drug products that contain clotrimazole. Assuming that there are about 25 affected OTC SKU's in the marketplace, total one-time costs of relabeling would be $50,000 to $75,000 if the manufacturers of these products changed their marketing from under an approved application to under the OTC drug monograph. In making this change, these manufacturers would save money by eliminating all costs associated with maintaining an application. Likewise, other manufacturers who now wish to market topical clotrimazole drug products will be able to enter the marketplace without the costs associated with an application. Their costs would involve the standard start-up costs of any OTC drug marketed under the monograph.

The agency considered but rejected several alternatives: (1) Not including clotrimazole in the monograph, (2) a longer implementation period, and (3) no interim marketing. The agency rejected the first alternative because it considers the data presented supportive of monograph status. The agency does not see a need for the second or third alternatives because these clotrimazole drug products are already marketed OTC under approved applications and compendial standards currently exist for clotrimazole. The agency does not consider an exemption for small entities necessary because those manufacturers can enter the marketplace under the monograph at any time.

Under the Unfunded Mandates Reform Act, FDA is not required to prepare a statement of costs and benefits for this proposed rule because this proposed rule is not expected to result in any one-year expenditure that would exceed $100 million adjusted for inflation.

This analysis shows that the agency has considered the burden to small entities. Thus, this economic analysis, together with other relevant sections of this document, serves as the agency's initial regulatory flexibility analysis, as required under the Regulatory Flexibility Act.

VI. Paperwork Reduction Act of 1995

FDA tentatively concludes that the labeling requirements for clotrimazole are not subject to review by the Office of Management and Budget because they do not constitute a ''collection of information'' under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the existing monograph labeling is a ''public disclosure of information originally supplied by the Federal Government to the recipient for the purpose of disclosure to the public'' (5 CFR 1320.3(c)(2)).

VII. Environmental Impact

The agency has determined under 21 CFR 25.31(a) 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.

VIII. Request for Comments

Interested persons may submit to the Dockets Management Branch (address above) written comments regarding the proposal by August 27, 2001. Written comments on the agency's economic impact determination may be submitted on or before August 27, 2001. Three copies of all comments are to be submitted, except that individuals may submit one copy. Comments 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. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

IX. Proposed Effective Date

The agency is proposing that any final rule that may issue based on this proposal become effective 30 days after its date of publication in the **Federal Register**.

List of Subjects in 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, it is proposed that 21 CFR part 333 be amended as follows:

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

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

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

2. Section 333.210 is amended by adding paragraph (g) to read as follows:

§ 333.210 Antifungal active ingredients.

* * * * *

(g) Clotrimazole 1 percent.

Dated: May 17, 2001.

Margaret M. Dotzel,

Associate Commissioner for Policy.

[FR Doc. 01–13299 Filed 5–25–01; 8:45 am]

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ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 52

[PA 169—4116; FRL–6986–8]

Approval and Promulgation of Air Quality Implementation Plans; Pennsylvania; Nitrogen Oxides Budget Trading Program

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: EPA is proposing to approve a State Implementation Plan (SIP) revision submitted by the Commonwealth of Pennsylvania on October 30, 2000 and April 4, 2001. This revision responds to the EPA's regulation entitled, ''Finding of Significant Contribution and Rulemaking for Certain States in the Ozone Transport Assessment Group Region for Purposes of Reducing Regional Transport of Ozone,'' otherwise known as the ''NO_X SIP Call.'' This revision establishes and requires a nitrogen oxides (NO_X) allowance trading program for large electric generating and industrial units, beginning in 2003. The intended effect of this action is to propose approval the Pennsylvania NO_X Budget Trading Program because it addresses the requirements of the NO_X SIP Call Phase I that will significantly reduce ozone transport in the eastern United States. EPA is proposing to approve this revision in accordance with the requirements of the Clean Air Act.

DATES: Written comments must be received on or before June 28, 2001.

ADDRESSES: Written comments should be mailed to David L. Arnold, Chief, Air Quality Planning and Information Services Branch, Mailcode 3AP21, U.S. Environmental Protection Agency, Region III, 1650 Arch Street, Philadelphia, Pennsylvania 19103. Copies of the documents relevant to this action are available for public inspection during normal business hours at the Air Protection Division, U.S. Environmental Protection Agency, Region III, 1650 Arch Street, Philadelphia, Pennsylvania 19103; and Pennsylvania Department of Environmental Protection, Bureau of Air Quality, P.O. Box 8468, 400 Market Street, Harrisburg, Pennsylvania 17105.

FOR FURTHER INFORMATION CONTACT: Cristina Fernandez, (215) 814–2178, or by e-mail at fernandez.cristina@epa.gov.

SUPPLEMENTARY INFORMATION: On October 30, 2000 and April 4, 2001, the Pennsylvania Department of Environmental Protection (PADEP) submitted a revision to the Pennsylvania SIP to address the requirements of the NO_X SIP Call Phase I. The information in this section is organized as follows:

I. EPA's Action

A. What action is EPA proposing today?
B. Why is EPA proposing this action?
C. What are the general NO_X SIP Call requirements?
D. What is EPA's NO_X budget trading program?
E. What guidance did EPA use to evaluate Pennsylvania's submittal?

II. Pennsylvania's NO_X Budget Trading Program

A. When did Pennsylvania submit the SIP revision to EPA in response to the NO_X SIP Call?
B. What is the Pennsylvania NO_X Budget Trading Program?
C. What is the result of EPA's evaluation of Pennsylvania's program?

III. Proposed Action

A. NO_X SIP Call Requirements
B. One-Hour Attainment Demonstration Plans

IV. Administrative Requirements

I. EPA's Action

A. What Action Is EPA Proposing Today?

EPA is proposing to approve the Pennsylvania SIP revision concerning the adoption of its NO_X Budget Trading Program, submitted on October 30, 2000 and April 4, 2001.

B. Why Is EPA Proposing This Action?

EPA is proposing this action for two purposes. Pennsylvania's NO_X Budget Trading Program regulations address the requirements of the NO_X SIP Call Phase I. In addition, Pennsylvania's NO_X Budget Trading Program regulations are part of the Pennsylvania one-hour ozone attainment demonstration plan for the Philadelphia-Wilmington-Trenton severe ozone nonattainment area. The Pennsylvania one-hour attainment demonstration plan for the Philadelphia-Wilmington-Trenton ozone nonattainment area relies on the NO_X reductions associated with the NO_X Budget Trading Program in 2003 and beyond. Therefore, EPA is proposing to approve Pennsylvania's NO_X Budget Trading Program for two reasons. First, because it addresses the requirements of the NO_X SIP Call Phase I, and secondly as a strengthening measure for the one-hour ozone standard attainment for Philadelphia-Wilmington-Trenton ozone nonattainment area.

C. What Are the General NO_X SIP Call Requirements?

On October 27, 1998, EPA published a final rule entitled, ''Finding of Significant Contribution and Rulemaking for Certain States in the Ozone Transport Assessment Group Region for Purposes of Reducing Regional Transport of Ozone,'' otherwise known as the ''NO_X SIP Call.'' See 63 FR 57356. The NO_X SIP Call requires 22 States and the District of Columbia to meet statewide NO_X emission budgets during the five month period between May 1 and October 1 in order to reduce the amount of ground level ozone that is transported across the eastern United States.

EPA determined state-wide NO_X emission budgets for each affected jurisdiction to be met by the year 2007. EPA identified NO_X emission reductions by source category that could be achieved by using cost-effective measures. The source categories included were electric generating units (EGUs), non-electric generating units (non-EGUs), area sources, nonroad mobile sources and highway sources. However, the NO_X SIP Call allowed states the flexibility to decide which source categories to regulate in order to meet the statewide budgets. In the NO_X SIP Call notice, EPA suggested that imposing statewide NO_X emissions caps on large fossil-fuel fired industrial boilers and electricity generating units would provide a highly cost effective means for States to meet their NO_X budgets. In fact, the state-specific budgets were set assuming an emission rate of 0.15 pounds NO_X per million British thermal units (lb. NO_X/mmBtu) at EGUs, multiplied by the projected heat input (mmBtu) from burning the quantity of fuel needed to meet the 2007 forecast for electricity demand. See 63 FR 57407. The calculation of the 2007 EGU emissions assumed that an emissions trading program would be part of an EGU control program. The NO_X SIP Call state budgets also assumed on average a 30% NO_X reduction from cement kilns, a 60% reduction from industrial boilers and combustion turbines, and a 90% reduction from internal combustion engines. The non-EGU control assumptions were applied at units where the heat input capacities were greater than 250 mmBtu per hour, or in cases where heat input data were