

DEPARTMENT OF HEALTH AND
HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 80N-0476]

RIN 0905-AA06

Topical Antifungal Drug Products for
Over-the-Counter Human Use; Certain
Labeling ClaimsAGENCY: Food and Drug Administration,
HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule establishing that certain labeling claims for over-the-counter (OTC) topical antifungal drug products are not generally recognized as safe and effective and are misbranded. FDA is issuing this final rule after considering the report and recommendations of the Advisory Review Panel on OTC Antimicrobial II Drug Products and public comments on an advance notice of proposed rulemaking and a notice of proposed rulemaking that were based on those recommendations. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: March 2, 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 public 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 March 12, 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 March 12, 1990. New data could have been submitted until December 12, 1990, and comments on the new data until February 12, 1991.

In evaluating OTC topical antifungal drug products, the Panel discussed ringworm of the scalp and ringworm of the nails (47 FR 12480 at 12487) and concluded:

Tinea capitis (ringworm of the scalp) and *tinea unguium* (ringworm of the nails). Fungal infections of the scalp and nails tend to be chronic. They respond poorly to topical therapy, partly because of the thickness of the nails and the depth of the hair roots. Both sites of infection provide inaccessible locations for fungi, thus drastically decreasing the penetration of topical antifungals. For this reason, OTC topical antifungals must be labeled that they are not effective for the treatment of ringworm of the scalp or nails.

The Panel recommended that the following labeling statement appear in the directions for all OTC topical antifungal drug products: "This product is not effective on the scalp or nails." (See 47 FR 12480 at 12566.)

No data were submitted in response to the Panel's report to support the use of OTC topical antifungal drug products on the scalp or the nails. However, one comment did request that the Panel's recommended statement "this product is not effective on the scalp or nails" be changed to read "this product is not effective in the treatment of fungal infections of the hair and nails." The agency responded that it was retaining the Panel's statement in the directions proposed in the tentative final monograph because the comment did not submit any data to support its suggested change. (See comment 32, 54 FR 51136 at 51155.)

In response to the tentative final monograph, one submission (Ref. 1) was received that contained clinical data to support the safety and effectiveness of a combination of antifungal and keratolytic ingredients for the topical treatment of fungal infections of the nails. The clinical data included the results of a double-blind, randomized,

clinical comparison of a product containing a combination of antifungal ingredients (undecylenic acid and chloroxylenol) and keratolytic ingredients (salicylic acid and acetic acid) to its vehicle containing isopropyl alcohol and benzocaine in the topical treatment of fungal infections of the toenails. This study had a major flaw in that it was not designed to demonstrate the contribution of each of the five active ingredients (undecylenic acid, acetic acid, salicylic acid, chloroxylenol, and benzocaine) to the effectiveness of the product's total formulation. The study should have included a comparison of the total formulation minus each of the active ingredients to the total formulation and to the vehicle in order to demonstrate the contribution of each of the active ingredients in the combination.

The clinical data also included the results of an open, uncontrolled study that did not provide any useful information to establish effectiveness. The agency's detailed comments and evaluation of the data are on file in the Dockets Management Branch (Ref. 2).

The agency is aware that a number of OTC topical antifungal drug products are currently being marketed with claims for use of the product on the scalp or on the nails. No evidence has been submitted to date to establish that any OTC topical antifungal drug products are effective for the treatment of fungal infections on the scalp or on the nails. The Commissioner has determined that OTC topical antifungal active ingredients are not generally recognized as safe and effective for use on the scalp or on the nails. Therefore, the Commissioner is issuing a separate final rule on all topical antifungal active ingredients present in any product bearing claims that it is indicated for the treatment of fungal infections on the scalp or on the nails. FDA has elected to act on OTC topical antifungal drug products bearing these claims before finalizing the rest of the monograph in order to expedite removal from the market of products that lack adequate evidence of effectiveness.

Any OTC topical antifungal drug product bearing any claims or directions for use of the product on the scalp or on the nails may not continue to be initially introduced or delivered for introduction into interstate commerce unless it is the subject of an approved application or abbreviated application (hereinafter called application). The agency is amending 21 CFR part 310 by adding to subpart E, new § 310.545(a)(22)(iii) (21 CFR 310.545(a)(22)(iii)) to include any topical antifungal drug products labeled

for use on the scalp or on the nails. Any claims or directions for using an OTC topical antifungal drug product on the scalp or on the nails should be eliminated from OTC drug products by March 2, 1994, regardless of whether further testing is undertaken to justify future use. Thereafter, any OTC drug product containing any topical antifungal active ingredient and labeled or intended for use on the scalp or on the nails will be considered nonmonograph and misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352) and a new drug under section 201(p) of the act (21 U.S.C. 321(p)) for which an approved application under section 505 of the act (21 U.S.C. 355) and 21 CFR part 314 of the regulations is required for marketing. Therefore, on or after March 2, 1994, no OTC drug product containing any OTC topical antifungal active ingredient labeled or intended for use on the scalp or on the nails 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 containing any active ingredient subject to this final rule that is repackaged or relabeled after the effective date of this final rule must be in compliance with the final rule regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are urged to comply voluntarily with this final rule at the earliest possible date.

The agency concludes that there is no basis for the continued marketing of any OTC topical antifungal drug products with claims or directions for use on the scalp or on the nails. The agency points out that publication of this final rule does not preclude a manufacturer's testing an antifungal ingredient for these uses. New, relevant data can be submitted to the agency at a later date as the subject of an application that may provide for prescription or OTC marketing status. (See 21 CFR part 314.) As an alternative, where there are adequate data establishing general recognition of safety and effectiveness for these uses, such data may be submitted in an appropriate citizen petition to amend the final monograph for OTC topical antifungal drug products. (See 21 CFR 10.30.) However, marketing of products containing topical antifungal active ingredients and bearing these claims may not begin or continue while the data are being evaluated by the agency.

References

- (1) Comment No. C30, Docket No. 80N-0476, Dockets Management Branch.
- (2) Letter from W. E. Gilbertson, FDA, to G. Mendoza, Kramer Laboratories, Inc., coded LET 24, Docket No. 80N-0476, Dockets Management Branch.

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). As a result of this final rule, some manufacturers will need to relabel their products to delete these claims and/or the directions for use related to these claims. The agency has identified about a dozen OTC topical antifungal drug products marketed with claims for use on the nails. All of these products will need to be relabeled. Based on information provided by a nonprescription drug manufacturer's association, the estimated average cost of a labeling revision is about \$2,000.00 per product label. Several of the currently marketed products will also need to be reformulated after the final monograph is issued because they either contain monograph ingredients at nonmonograph concentrations or contain combinations of ingredients that are not included in the final monograph. All products can be reformulated to allowable monograph conditions and remain in the marketplace with appropriate relabeling. The cost of reformulation 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.

Early finalization of the nonmonograph status of the claims listed in this notice will benefit both consumers and manufacturers. Consumers will benefit from the early removal from the marketplace of product claims for which safety and effectiveness have not been established. This will result in a direct economic savings to consumers. Manufacturers of products with such claims will benefit from being able to use alternative claims that have been proposed and will be recognized by the agency as being generally recognized as safe and effective, without incurring additional expense of clinical testing to support these claims. (See proposed § 333.250(b), 54 FR 51136 at 51161.) Based on the information above, 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.

List of Subjects in 21 CFR Part 310

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

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 310 is amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 is revised 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).

2. Section 310.545 is amended by adding new paragraph (a)(22)(iii), by revising the introductory text of paragraph (d), and by adding new paragraph (d)(12) to read as follows:

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

(a) * * *

(22) * * *

(iii) Any ingredient(s) labeled with claims or directions for use on the scalp or on the nails.

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(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)(12) of this section.

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(12) March 2, 1994, for products subject to paragraph (a)(22)(iii) of this section.

Dated: August 26, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

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