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By the Commission.

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Margaret H. McFarland,

Deputy Secretary.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310 and 358

[Docket No. 02N-0359]

RIN 0910-AA01

Ingrown Toenail Relief Drug Products for Over-the-Counter Human Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule establishing conditions under which over-the-counter (OTC) ingrown toenail relief drug products containing sodium sulfide 1 percent in a gel vehicle are generally recognized as safe and effective and not misbranded. This rule also amends the regulation that lists nonmonograph active ingredients in OTC drug products for ingrown toenail relief by removing sodium sulfide from that list. This final rule is part of FDA's ongoing review of OTC drug products.

DATES: This rule is effective June 6, 2003.

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 9, 1993 (58 FR 47602), FDA published a final rule establishing that any ingrown toenail relief drug product for OTC human use is not generally recognized as safe and effective and is misbranded. (See 21 CFR 310.538.) In that final rule, sodium sulfide 1 percent was considered effective but not safe for the temporary relief of pain associated with ingrown toenails because of its potential for causing adverse reactions, particularly burning sensations and skin irritation.

In the **Federal Register** of October 4, 2002 (67 FR 62218), after reviewing new data that had been submitted, FDA proposed to establish conditions under which OTC ingrown toenail relief drug products containing sodium sulfide 1 percent in a gel vehicle are generally recognized as safe and effective and not misbranded. The product is used with a retainer ring to keep the product at the area of application. The agency also proposed to amend the regulation (21 CFR 310.538) that lists nonmonograph active ingredients in OTC drug products for ingrown toenail relief by removing sodium sulfide from that list.

II. Comments Received in Response to the Proposal

In response to the proposal, the agency received two comments, which are on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. One comment, from a drug manufacturer, supported the agency's proposals and requested that the agency's review of the comments and publication of the final rule be completed as expeditiously as possible. The second comment, from a consumer, stated that the use of the product with a "restraining" ring as indicated should have a "green light." The comment added that there are many people who experience the pain of an ingrown toenail, and that these products will help.

III. The Agency's Final Conclusions

The agency concludes that the data support OTC drug monograph status for 1 percent sodium sulfide in a gel vehicle applied topically for the relief of discomfort (pain) of ingrown toenail. The product is used with a retainer ring to keep the product at the area of application. Accordingly, the agency is proposing a new monograph in part 358, subpart D (21 CFR part 358, subpart D) for ingrown toenail relief drug products that includes 1 percent sodium sulfide gel. The agency is also amending § 310.538 to state that it no longer applies to sodium sulfide.

Mandating warnings in an OTC drug monograph does not require a finding that any or all of the OTC drug products covered by the monograph actually caused an adverse event, and FDA does not so find. Nor does FDA's requirement of warnings repudiate the prior OTC drug monographs and monograph rulemakings under which the affected drug products have been lawfully marketed. Rather, as a consumer protection agency, FDA has determined that warnings are necessary to ensure

that these OTC drug products continue to be safe and effective for their labeled indications under ordinary conditions of use as those terms are defined in the Federal Food, Drug, and Cosmetic Act. This judgment balances the benefits of these drug products against their potential risks (see 21 CFR 330.10(a)).

FDA's decision to act in this instance need not meet the standard of proof required to prevail in a private tort action (*Glastetter v. Novartis Pharmaceuticals, Corp.*, 252 F.3d 986, 991 (8th Cir. 2001)). To mandate warnings, or take similar regulatory action, FDA need not show, nor do we allege, actual causation. For an expanded discussion of case law supporting FDA's authority to require such warnings, see Labeling of Diphenhydramine-Containing Drug Products for Over-the-Counter Human Use, Final Rule (67 FR 72555, December 6, 2002).

IV. Analysis of Impacts

FDA has examined the impacts of this final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (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 of 1995 requires that agencies prepare a written statement of anticipated costs and benefits 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 final rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. FDA has determined that the final rule is not a significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order. As explained later in this section, FDA concludes that the final rule will not have a significant economic impact on a substantial number of small entities. The Unfunded Mandates Reform Act