

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310 and 358

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Certifier A. Corbin

[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 [*insert date 30 days after date of publication in the Federal Register*].

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:

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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 does not require FDA to prepare a statement of costs and benefits for this final rule, because the rule is not expected to result in any 1-year expenditure that would exceed \$100 million adjusted for inflation. The current inflation adjusted statutory threshold is about \$110 million.

The purpose of this final rule is to establish a monograph for ingrown toenail relief drug products for OTC human use and include sodium sulfide 1 percent in a gel vehicle in the monograph. This final rule provides for OTC availability of this type of product.

Manufacturers who wish to market this type of product have the standard costs associated with the introduction of any new product. These include preparation of labeling, stability testing, and implementing manufacturing procedures. Any cost incurred will be voluntary if manufacturers elect to market this type of product. This cost may vary from manufacturer to manufacturer; however, the burden on small manufacturers is not greater than that for large manufacturers. Manufacturers will not incur any costs related to proving safety and effectiveness of the active ingredient for this intended use.

Under the Regulatory Flexibility Act, if a rule has a significant impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of a rule on small entities. This final rule allows manufacturers to market OTC ingrown toenail relief drug products containing sodium sulfide 1 percent in a gel vehicle without having to obtain an approved new drug application, as is currently required, and is beneficial to small entities. Thus, this final rule will not impose a significant economic burden on affected entities. Therefore, under the Regulatory

Flexibility Act, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities. No further analysis is required.

V. Paperwork Reduction Act of 1995

FDA concludes that the labeling requirements in this document 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 labeling statements are 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)).

VI. 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.

VII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive

order and, consequently, a federalism summary impact statement is not required.

List of Subjects

21 CFR Part 310

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

21 CFR Part 358

Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 310 and 358 are amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b–360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b–263n.

2. Section 310.538 is amended by removing the ingredient sodium sulfide in paragraph (a) and by adding paragraph (e) to read as follows:

§ 310.538 Drug products containing active ingredients offered over-the-counter (OTC) for use for ingrown toenail relief.

* * * * *

(e) This section does not apply to sodium sulfide labeled, represented, or promoted for OTC topical use for ingrown toenail relief in accordance with part 358, subpart D of this chapter, after [*insert date 30 days after date of publication in the Federal Register*].

PART 358—MISCELLANEOUS EXTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

3. The authority citation for 21 CFR part 358 continues to read as follows:

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

4. Part 358 is amended by adding new subpart D, consisting of §§ 358.301 to 358.350, to read as follows:

Subpart D—Ingrown Toenail Relief Drug Products

Sec.

358.301 Scope.

358.303 Definitions.

358.310 Ingrown toenail relief active ingredient.

358.350 Labeling of ingrown toenail relief drug products.

Subpart D—Ingrown Toenail Relief Drug Products

§ 358.301 Scope.

(a) An over-the-counter ingrown toenail relief drug product in a form suitable for topical administration is generally recognized as safe and effective and is not misbranded if it meets each condition in this subpart and each general condition established in § 330.1 of this chapter.

(b) References in this subpart to regulatory sections of the Code of Federal Regulations are to chapter 1 of title 21 unless otherwise noted.

§ 358.303 Definitions.

As used in this subpart:

(a) *Ingrown toenail relief drug product.* A drug product applied to an ingrown toenail that relieves pain or discomfort either by softening the nail or by hardening the nail bed.

(b) *Retainer ring.* A die cut polyethylene foam pad coated on one side with medical grade acrylic pressure-sensitive adhesive. The retainer ring has slots, center-cut completely through the foam with the cut of sufficient size to allow for localization of an active ingredient in a gel vehicle to a specific target area. The retainer ring is used with adhesive bandage strips to place over the retainer ring to hold it in place.

§ 358.310 Ingrown toenail relief active ingredient.

The active ingredient of the product is sodium sulfide 1 percent in a gel vehicle. The gel vehicle is an aqueous, semisolid system with large organic molecules interpenetrated with a liquid.

§ 358.350 Labeling of ingrown toenail relief drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the product, if any, and identifies the product as an “ingrown toenail relief product” or as an “ingrown toenail discomfort reliever.”

(b) *Indications.* The labeling of the product states, under the heading “Use,” the following: “for temporary relief of” [select one or both of the following: ‘pain’ or ‘discomfort’] “from ingrown toenails”. Other truthful and nonmisleading statements, describing only the use that has been established and listed in this paragraph (b), may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(c) *Warnings.* The labeling of the product contains the following warnings under the heading “Warnings”:

(1) “For external use only” in accord with § 201.66(c)(5)(i) of this chapter.

(2) “Do not use [bullet]¹ on open sores”.

(3) “Ask a doctor before use if you have [bullet] diabetes [bullet] poor circulation [bullet] gout”.

(4) “When using this product [bullet] use with a retainer ring”.

(5) “Stop use and ask a doctor if [bullet] redness or swelling of your toe increases [bullet] discharge is present around the nail [bullet] symptoms last more than 7 days or clear up and occur again within a few days”.

(d) *Directions.* The labeling of the product contains the following statements under the heading “Directions”:

(1) “[Bullet] adults and children 12 years and over:”

(i) “[Bullet] wash the affected area and dry thoroughly [bullet] place retainer ring on toe with slot over the area where the ingrown nail and the skin meet. Smooth ring down firmly. [bullet] apply enough gel product to fill the slot in the ring [bullet] place round center section of bandage strip directly over the gel-filled ring to seal the gel in place. Smooth ends of bandage strip around toes.”

(ii) “[Bullet] repeat twice daily (morning and night) for up to 7 days until discomfort is relieved or until the nail can be lifted out of the nail groove and easily trimmed”.

(2) “[Bullet] children under 12 years: ask a doctor”.

¹See § 201.66(b)(4) of this chapter for definition of bullet.

Dated: 4/23/03
April 23, 2003.



Jeffrey Shuren,
Assistant Commissioner for Policy.

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