DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 80N–0348]

RIN 0905–AA06

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 that any ingrown toenail relief drug product for over-the-counter (OTC) human use is not generally recognized as safe and effective and is misbranded. FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and all new data and information on OTC ingrown toenail relief drug products that have come to the agency's attention. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: March 9, 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 October 17, 1980 (45 FR 69128), 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 ingrown toenail relief drug products, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous External 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 January 15, 1981. Reply comments in response to comments filed in the initial comment period could be submitted by February 16, 1981.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were placed on display in the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857, after deletion of a small amount of trade secret information.

The agency's proposed regulation, in the form of a tentative final monograph, for OTC ingrown toenail relief drug products was published in the **Federal Register** of September 3, 1982 (47 FR 39120). Interested persons were invited to file by November 2, 1982, 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 January 2, 1983. New data could have been submitted until September 3, 1983, and comments on the new data until November 3, 1983.

In the **Federal Register** of November 7, 1990 (55 FR 46914), the agency published a final rule in 21 CFR part 310 establishing that certain active ingredients that had been under consideration in a number of OTC drug rulemaking proceedings were not generally recognized as safe and effective. That final rule was effective on May 7, 1991, and included, in § 310.545(a)(11), chloroxylenol and urea, active ingredients under consideration in the rulemaking for OTC ingrown toenail relief drug products. These ingredients were determined to be nonmonograph because no additional data had been submitted establishing that they were generally recognized as safe and effective for ingrown toenail relief. Final agency action on all other OTC ingrown toenail relief drug products occurs with the publication of this final rule.

In the proposed rule, the agency did not propose any OTC ingrown toenail relief active ingredient as generally recognized as safe and effective and not misbranded. However, the agency proposed monograph labeling in the event that data were submitted that resulted in the upgrading of any ingredient to monograph status in the final rule. In this final rule, however, no ingredient has been determined to be generally recognized as safe and effective for use in OTC ingrown toenail relief drug products. Therefore, proposed subpart D of 21 CFR part 358 for OTC ingrown toenail relief drug products is not being issued as a final regulation.

This final rule declares OTC drug products containing active ingredients for ingrown toenail relief to be new drugs under section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)), for which an application or abbreviated application (hereinafter called application) approved under section 505 of the act (21 U.S.C. 355) and 21 CFR part 314 is required for marketing. In the absence of an approved application, products containing these drugs for this use also would be misbranded under section 502 of the act (21 U.S.C. 352). In appropriate circumstances, a citizen petition to establish a monograph may be submitted under 21 CFR 10.30 in lieu of an application.

This final rule amends 21 CFR part 310 to include drug products containing ingrown toenail relief ingredients by adding new § 310.538 (21 CFR 310.538) to subpart E. The inclusion of OTC ingrown toenail relief drug products in part 310 follows FDA's established policy for regulations in which there are no monograph conditions. (See, e.g., §§ 310.510, 310.519, 310.525, 310.526, 310.532, 310.533, and 310.534.) If, in the future, any ingredient is determined to be generally recognized as safe and effective for use in an OTC ingrown toenail relief drug product, the agency will promulgate an appropriate regulation at that time.

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 does not 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. In place of Category I, the term "monograph conditions" is used; in place of Categories II or III, the term "nonmonograph conditions" is used.

In the proposed regulation for OTC ingrown toenail relief drug products (47 FR 39120), the agency advised that it would provide a period of 12 months after the date of publication of the final monograph in the **Federal Register** for relabeling and reformulation of ingrown toenail relief drug products to be in compliance with the monograph. Although data and information were submitted on tannic acid and sodium sulfide 1 percent in response to the proposed rule, they were not sufficient to support monograph conditions, and no monograph is being established at this time. Therefore, ingrown toenail relief drug products that are subject to this rule are not generally recognized as safe and effective and are misbranded (nonmonograph conditions). In the advance notice of proposed rulemaking

(45 FR 69128), the agency advised that conditions excluded from the monograph (Category II) would be effective 6 months after the date of publication of a final monograph in the **Federal Register**. Because no OTC drug monograph is being established for this class of drug products, the agency is adopting this 6-month effective date for the nonmonograph conditions for these drug products. Therefore, on or after March 9, 1994, no OTC drug products that are subject to this final monograph may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved application.

In response to the proposed rule on OTC ingrown toenail relief drug products, two drug manufacturers submitted comments. Copies of the comments received are on public display in the Dockets Management Branch (address above). Additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch.

I. The Agency's Conclusions on the Comments

A. Comments on Ingredients

1. One comment requested Category I status for tannic acid contending that it has the capability to harden the nail groove by hardening the skin around the nail, which the Panel considered the prime treatment consideration in relief of ingrown toenail (45 FR 69128 at 69131). The comment reviewed the Panel's assessment of tannic acid and disagreed with the agency's assessment of data discussed in the tentative final monograph (comment 5, 47 FR 39120 at 39122).

The comment submitted clinical data (Refs. 1 and 2) to support the epidermal hardening action of tannic acid. One study (Ref. 1) was a double-blind, randomized, parallel, multi-centered, outpatient study of 53 subjects who applied 25 percent tannic acid in isopropyl alcohol (83 percent by volume) or isopropyl alcohol (83 percent by volume) alone to their ingrown toenails 3 or 4 times a day. Symptoms were evaluated during the initial visit, after 7 days, and at the completion of the 14-day study. The study evaluated epidermal hardening, tenderness, infection, skin temperature, inflammation, edema, nail-flap hypertrophy, and cellulitis. At the completion of the study, global evaluations were made by both the investigator and the subjects using a scale of 1 to 6 with a score of 1 equal to complete clinical control of the condition, a score of 5 equal to exacerbation of the condition, and a score of 6 representing no evaluation. In addition, each subject was provided with a self-rating daily diary and instructed to record the relief of pain, swelling, and redness, using a four-point scale: none, mild, moderate, and severe.

The comment submitted the results of a second double-blind, randomized, parallel study of 42 subjects using a modified in vivo technique (Ref. 2) to substantiate the epidermal hardening effect of tannic acid. The technique utilized blunt (nonabrasive) probes connected to a desktop computer terminal to objectively determine skin softness and smoothness. Subjects applied either 25 percent tannic acid in 83 percent isopropyl alcohol (21 subjects) or 83 percent isopropyl alcohol alone (21 subjects) 3 or 4 times daily for 7 days. Epidermal hardening was measured on the skin proximal to an ingrown toenail and at a control site on each subject on the initial visit and again after 7 days. The comment contended that the study's results demonstrate a statistically significant hardening effect of the tannic acid solution on skin surrounding ingrown toenails with a p-value of .008.

As discussed in the tentative final monograph (47 FR 39120 at 39122), the agency concurs with the Panel that evidence was insufficient to show that tannic acid is effective in relieving the symptoms of ingrown toenail by hardening the skin and shrinking the soft tissue surrounding an ingrown toenail because the studies submitted to the Panel did not test tannic acid alone. The agency has reviewed the new clinical data and determined that they also are inadequate to support the effectiveness of tannic acid for the relief of ingrown toenails. In the first study (Ref. 1), the subjects selected were to have been classified as having "mild to moderate ingrown toenail" or "acute mild to moderate ingrown toenail," yet several subjects in the study had ingrown toenails for long periods of time (ranging up to 3 years), and one subject had had previous surgery and was without a nail. Thus, it was not clear what is meant by "acute, mild to moderate" ingrown toenail and it appears that some of the subjects were not appropriately included in the study. Subject selection was to be based on both inclusion characteristics (age and nail involvement) and exclusion characteristics (pregnancy, preexisting diseases, sensitivities, deformed nails, and infection). These criteria were not followed. Of the 53 subjects in the study, 14 should not have been included according to the protocol.

Target symptoms and parameters were evaluated on three visits; however, the grading scale was highly subjective with inconsistencies occurring between investigators and between investigators and subjects. Adjunctive therapy, including sandals, open toe shoes, and cut shoes, was used in a least 11 subjects with no evaluation made of the effects of this additional treatment.

The statistical analysis and conclusions addressed only a few of the test parameters. Comparisons of nail-flap hypertrophy, nail-cutting difference, pain difference, and redness difference were not made between the second and third visits and overall. The agency concludes that in a study to demonstrate the "relief of symptoms of ingrown toenail," all data for all symptoms used as test parameters need to be included and considered.

While the study's conclusions were drawn from 47 of the 53 subjects enrolled, data from only 26 subjects can be considered due to both protocol and investigational discrepancies on 27 subjects. Even if only the 26 subjects who meet the protocol were considered, 50 percent or greater relief of symptoms was obtained in 28 percent of the tannic acid group compared to 34 percent of the control group. Therefore, it could be argued that the base was more effective than the tannic acid.

In the second study (Ref. 2), the comment contends that the study shows a 46 percent increase in skin hardness for the tannic acid group and a 6 percent decrease in skin hardness for the alcohol-control group. The agency notes, however, that no other symptoms of ingrown toenail relief were assessed. While the study may provide support for tannic acid as a "skin hardener," it is not acceptable as adequate proof of effectiveness for tannic acid for the relief of other symptoms of ingrown toenail, such as pain, inflammation, and tenderness.

Although the comment contends that tannic acid hardens epidermal tissue and reduces inflammation significantly better than the base alone, the submitted studies do not show significant differences in favor of tannic acid. Based on the deficiencies in both studies, as noted above, the agency concludes that these data are not acceptable as adequate proof of effectiveness that tannic acid relieves symptoms of ingrown toenails.

References

(1) "A Comparison of the Efficacy of Tannic Acid in Isopropyl Alcohol versus Isopropyl Alcohol Base for Relief of

Discomfort of Ingrown Toenail," Comment No. C00007, Docket No. 80N–0348, Dockets Management Branch.

(2) "Double Blind, Randomized Parallel Study of the Effect of a Tannic Acid Solution on the Hardness of the Skin of People with Onychocryptosis," Comment No. C00009, Docket No. 80N–0348, Dockets Management Branch.

2. One comment submitted data (Ref. 1) to support the use of sodium sulfide 1 percent for the temporary relief of pain associated with ingrown toenails. In addition, the comment stated that the data support an expanded indications statement for products containing sodium sulfide: "Relieves pain by softening imbedded (ingrown) toenails." The data resulted from a well-controlled, double-blind, multicenter clinical study involving a total of 61 subjects in two separate trials. In both trials, the test subjects applied sodium sulfide 1 percent for 7 days, while the control subjects used a placebo consisting of the identical vehicle without the active ingredient. One of the subjects treated two toes, while another subject dropped out after 5 days.

The agency has evaluated the results of the study and determined that they demonstrate that sodium sulfide 1 percent, when compared to placebo, is effective in providing temporary relief of pain due to ingrown toenails. The difference was shown to be statistically significant (p = less than .001). The sodium sulfide treated group showed a decrease in pain beginning on day 2, with continuing decrease in pain throughout the remaining 5 days of the study. The placebo group did not improve significantly throughout the 7-day study period.

The data also show that the nails of the test subjects who used sodium sulfide 1 percent were softened beginning on day 2, with improvement to day 6, but with no significant improvement thereafter. However, the study did not clearly establish that the symptomatic relief reported was due to softening of the imbedded (ingrown) toenail. Subjects receiving the placebo also showed a slight but not significant increase in nail softness by days 4, 6, and 7 compared to day 1.

In reviewing the data, the agency noted that in both trials many of the subjects using the test drug product suffered adverse effects. This raised questions about the safety of using sodium sulfide for the relief of pain associated with ingrown toenails.

In the first trial consisting of 32 subjects, 15 used the sodium sulfide product and 17 used the placebo. One subject using the sodium sulfide drug product dropped out of the study after day 5 because of erosions that failed to heal within 24 hours. Seven of the subjects using the sodium sulfide product experienced mild to moderate adverse reactions such as tingling, stinging sensation, and/or slight to severe burning sensations. Four of the subjects using the placebo also reported some mild adverse reactions, such as stinging, throbbing, swelling, numbness, and/or rash.

In the second trial, 29 subjects completed the study. Fourteen subjects used the sodium sulfide product, and 15 subjects used the placebo. Five of the subjects using sodium sulfide reported severe adverse reactions, such as burning, "open and sore," "red and open," and slight erythema. Three subjects stopped using the sodium sulfide product temporarily. Three other subjects using the sodium sulfide product experienced mild reactions, such as slight burning or tingling.

In summary, 16 of the 29 subjects using the sodium sulfide product in the two trials experienced some type of adverse reaction. The agency could not clearly ascertain from the clinical data submitted what proportion of the adverse reactions may have been drug induced. However, many of the subjects were advised to use vaseline, stop using the product, and/or use soapy soaks and epsom salts.

The agency concludes that the extremely high incidence of adverse reactions, particularly the burning sensations and irritation, and the need for subsequent professional advice and counseling to counter the effects of these adverse reactions makes this ingredient unacceptable for OTC use. The agency considers sodium sulfide as unsafe for OTC human use for the temporary relief of pain associated with ingrown toenails, Therefore, sodium sulfide 1 percent is not considered a monograph condition.

Reference

(1) "New Clinical Data Supporting Efficacy of Sodium Sulfide, 1 percent in Relieving Pain of Ingrown Toenails," Comment No. C00008, Docket No. 80N–0348, Dockets Management Branch.

3. One manufacturer requested a meeting to discuss protocols for studies to support the safety and effectiveness of an anesthetic in combination with tannic acid (Ref. 1).

The agency requested the manufacturer to provide proposed protocols (Refs. 2 and 3), but none have been submitted to date. The use of several anesthetic ingredients (benzocaine, chlorobutanol, and dibucaine) in ingrown toenail relief drug products was discussed by the Panel (45 FR 69122 at 69129) and their review was deferred to the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products. That Panel did not review these ingredients for this use. The agency is not aware of any data that establish the safety and effectiveness of anesthetic ingredients for the relief of symptoms (e.g., pain) of ingrown toenail. Therefore, benzocaine, chlorobutanol, and dibucaine are nonmonograph conditions for this use.

References

(1) Comment No. C00010, Docket No. 80N0348, Dockets Management Branch.

(2) Letter from W. E. Gilbertson, FDA, to C. Farhi, American Home Products Corp., coded ANS/C00010, Docket No. 80N–0348, Dockets Management Branch.

(3) Letter from W. E. Gilbertson, FDA, to C. Farhi, American Home Products Corp., coded LET2, Docket No. 80N–0348, Dockets Management Branch.

B. Comments on Directions

4. One comment requested revisions in the directions for use for OTC ingrown toenail drug products. The comment noted that it used these suggested directions in a clinical study and they were easy for consumers to understand. A second comment requested that the directions provide the option of applying ingrown toenail relief drug products with an applicator or with cotton in the nail groove.

The agency is not addressing these comments in this final rule because no active ingredients are included in a monograph for OTC ingrown toenail relief drug products. When an active ingredient achieves Category I status for this use, the agency will develop appropriate directions for use and will consider the comments' requests at that time.

II. The Agency's Final Conclusions on OTC Ingrown Toenail Relief Drug Products

At this time, there is a lack of sufficient data to establish that benzocaine, chlorobutanol, dibucaine, sodium sulfide, tannic acid, or any other ingredients are safe and effective for use for ingrown toenail relief. The agency has determined that no active ingredient has been found to be generally recognized as safe and effective and not misbranded for use in an OTC ingrown toenail relief drug product.

In the **Federal Register** of November 7, 1990 (55 FR 46914), the agency published a final rule in part 310 establishing that certain active ingredients that had been under consideration in a number of OTC drug

rulemaking proceedings were not generally recognized as safe and effective. That final rule was effective on May 7, 1991, and included in § 310.545(a)(11) the ingredients chloroxylenol and urea that had been previously considered under this rulemaking for use as active ingredients in ingrown toenail relief drug products. This final rule establishes that any OTC ingrown toenail relief drug product is not generally recognized as safe and effective and expands the nonmonograph ingredients to include all other OTC ingrown toenail relief active ingredients. These additional ingredients include, but are not limited to, benzocaine, chlorobutanol, dibucaine, sodium sulfide, and tannic acid, which were reviewed by the Panel and the agency. Therefore, any ingredient that is labeled, represented, or promoted for use as an ingrown toenail relief drug product is considered nonmonograph and misbranded under section 502 of the act and is a new drug under section 201(p) of the act for which an approved application under section 505 of the act and 21 CFR part 314 of the regulations is required for marketing. In appropriate circumstances, a citizen petition to establish a monograph may be submitted under 21 CFR 10.30 in lieu of an application. Any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce after the effective date of the final rule that is not in compliance with the regulation is subject to regulatory action. In order to avoid duplication in listing OTC ingrown toenail relief active ingredients in more than one regulation and for ease in locating these ingredients in the Code of Federal Regulations, the agency is listing all of these ingredients in a single regulation in new § 310.538 entitled "Drug products containing active ingredients offered over-the-counter (OTC) for use for ingrown toenail relief." Accordingly, § 310.545(a)(11) is being removed.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (47 FR 39120 at 39124). The agency has examined the economic consequences of this final rule 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 final rule for OTC ingrown toenail relief drug products, 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 ingrown toenail relief drug products is not expected to pose such an impact on small businesses because only a limited number of products are affected. As noted above, the ingredients chloroxylenol and urea have already been removed from OTC ingrown toenail relief drug products. The submitted product that contained sodium sulfide is not currently marketed. The agency is only aware of a few products containing other ingredients (e.g., two combination drug products containing chlorobutanol and tannic acid, and one containing benzocaine and tannic acid). Based on the limited number of affected products, 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 continues 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. New § 310.538 is added to subpart E to read as follows:

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

(a) Any product that bears labeling claims such as for "temporary relief of discomfort from ingrown toenails," or "ingrown toenail relief product," or "ingrown toenail reliever," or similar claims is considered an ingrown toenail relief drug product. Benzocaine, chlorobutanol, chloroxylenol, dibucaine, sodium sulfide, tannic acid, and urea have been present as ingredients in such products. There is lack of adequate data to establish general recognition of the safety and effectiveness of these or any other ingredients for OTC use for ingrown toenail relief. Based on evidence currently available, any OTC drug product containing ingredients offered for use for ingrown toenail relief cannot be generally recognized as safe and effective.

(b) Any OTC drug product that is labeled, represented, or promoted for ingrown toenail relief is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act), for which an approved application or abbreviated application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved new drug application or abbreviated new drug application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for OTC use for ingrown toenail relief is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) After March 9, 1994, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

§ 310.545 [Amended]

3. Section 310.545 *Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses* is amended by removing and reserving paragraph (a)(11).

Dated: September 2, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

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