DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 358

[Docket No. 80N-0348]

Ingrown Toenail Relief Drug Products for Over-the-Counter Human Use; Tentative Final Monograph

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) ingrown toenail relief drug products are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products and the public comments on an advance notice of proposed rulemaking that was based on those recommendations. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs on the proposed regulation by November 2, 1982. New data by September 3, 1983.

Comments on the new data by November 3, 1983. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Comments on the agency's economic impact determination by January 2, 1983.

ADDRESS: Written comments, objections, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857. New data and comments on new data should also be addressed to the Dockets Management Branch.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, National Center for Drugs and Biologists (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

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, 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 put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information.

The advance notice of proposed rulemaking, which was published in the **Federal Register** on October 17, 1980 (45 FR 69128), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the present document is designated in the OTC drug review regulations as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule) the FDA states for the first time its position on the establishment of a monograph for OTC ingrown toenail relief drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC ingrown toenail relief drug products.

In response to the advance notice of proposed rulemaking, two consumers, two drug manufacturers, and one college of podiatric medicine submitted comments. Copies of these comments are on public display in the Dockets Management Branch.

This proposal would amend Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations in Part 358 by adding Subpart D. This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC ingrown toenail relief drug products as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report. Modifications have been made for clarity and regulatory accuracy and are reflected in this tentative final monograph. The agency emphasizes that no ingrown toenail relief active ingredients have been determined to be generally recognized as safe and effective and not misbranded. However, the agency is proposing Category I labeling in this document in the event that data are submitted which result in the upgrading of any ingredient to monograph status in the final rule.

FDA published in the **Federal Register** of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision is now deleted from the regulations. The regulations 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 (46 FR 47738).

Although it was not required to do so under *Cutler*, FDA will no longer use the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the **Federal Register**. On or after that date, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved new drug application. Further, any OTC drug products subject to this monograph that are repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In the advance notice of proposed rulemaking for OTC ingrown toenail relief drug products (published in the **Federal Register** of October 17, 1980 (45 FR 69128)), the agency had suggested that the conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the **Federal Register** and that the conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of whether further testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products will have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and if further reformulation is required, there could be a further delay in having a new product available for manufacture.

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss, but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the **Federal Register**. The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and have their products in compliance in the marketplace. However, if the agency determines that any labeling for a condition included in the final monograph should be implemented sooner, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notices published in the **Federal Register** of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

I. The Agency's Tentative Conclusions on the Comments

A. General Comment on Ingrown Toenail Relief Drug Products

1. One comment questioned how the government could become involved in such a trivial matter as proposing a rule on ingrown toenail relief drug products. The comment requested that the agency not issue this rule.

As part of the agency's review of all OTC drug products, the Panel considered the safety and effectiveness of many classes of OTC miscellaneous external drug products. Although ingrown toenail relief drug products affect only a small group of consumers, the agency believes that all marketed OTC drug products should be both safe and effective and not misbranded for their intended use. Accordingly, the agency is continuing with this rulemaking proceeding.

B. Comments on Ingrown Toenail Relief Ingredients

2. One comment contended that the existing clinical data reviewed by the Panel (Ref. 1) sufficiently demonstrated the efficacy of a 1-percent concentration of sodium sulfide in relieving pain and tenderness associated with ingrown toenails. However, the comment stated that an additional clinical study would be provided to the agency to demonstrate the efficacy of sodium sulfide in treating ingrown toenails.

The agency has evaluated the clinical data reviewed by the Panel and agrees with the Panel that they are not sufficient to establish the effectiveness of 1 percent sodium sulfide for the temporary relief of discomfort due to ingrown toenails. The additional clinical study referred to by the comment has not been submitted yet. In the absence of new clinical data demonstrating the effectiveness of 1 percent sodium sulfide, this ingredient will remain in Category III, as recommended by the Panel.

Reference

(1) OTC Volumes 160100 and 160280.

3. One comment questioned the Panel's conclusion that tannic acid is safe in concentrations up to 25 percent when applied to the area of an ingrown toenail. The comment noted the Panel's recommended warning against the use of a tannic acid product on open sores, but contended that an ingrown toenail could cause a hard-to-detect puncture of the skin through which tannic acid could be absorbed and thereby cause liver damage.

The Panel stated that tannic acid has little action on intact skin and that it is safe when applied to a small area of intact skin such as that surrounding an ingrown toenail. Similarly, the Antimicrobial II Panel concluded in its report on OTC antifungal drug products (published in the **Federal Register** of March 23, 1982; 47 FR 12480) that topically applied tannic acid is likely to interact with surface proteins so extensively that even when used on the fissured areas of athlete's foot, percutaneous absorption of this ingredient is unlikely. The agency believes that in the case of a small puncture of the skin that may be caused by an ingrown toenail, a smiliar reaction will result, and absorption is unlikely to occur. Further, because only a few drops of tannic acid solution would be used on an ingrown toenail, the agency believes that tannic acid is safe in concentrations up to 25 percent when application is limited to this small area.

4. One comment requested that tannic acid be included in the tentative final monograph and disputed the Panel's conclusion that there is insufficient evidence to show that tannic acid alone is effective in hardening the skin and shrinking soft tissue surrounding the ingrown toenail. The comment cited a study by Grinell (Ref. 1), in which 44 subjects used a product containing a combination of tannic acid and chlorobutanol in isopropyl alcohol, and studies in mice comparing tannic acid in isopropyl alcohol to the tannic acid and chlorobutanol combination in isopropyl alcohol (Ref. 2). The comment, noting Grinell's conclusion that the tannic acid-chlorobutanol combination product was effective in reducing pain and helping to restore the nail to its proper relationship with soft toe tissues, added that although tannic acid was not studied alone, it is the only ingredient in the combination capable of hardening the nail groove by hardening the skin around the nail. The comment contended that hardening the surrounding skin is the main consideration in relieving ingrown toenail.

The agency has reviewed the data submitted and concurs with the Panel's conclusion. Because these studies did not test tannic acid alone, there is insufficient evidence to show that this ingredient is effective in relieving the symptoms of ingrown toenail by hardening the skin and shrinking the soft tissue surrounding an ingrown toenail. Controlled clinical studies are needed to show the effect of tannic acid alone in relieving ingrown toenail symptoms.

References

(1) Grinell, R. N., "Ingrown Toe Nail," *Podiatry Quarterly*, 2:8–10, 1964.
(2) OTC Volume 160384.

5. One comment requested that the combination of tannic acid and chlorobutanol in isopropyl alcohol be placed in Category I for the relief of ingrown toenail. Citing data submitted to the Panel (Ref. 1), the comment contended that tannic acid hardens the skin of the nail groove surrounding an ingrown toenail to help restore the normal relationship of the nail to the surrounding soft tissue, and that chlorobutanol is a local anesthetic for relief of pain.

After reviewing the data submitted to the Panel, the agency believes that such a combination appears rational for the relief of ingrown toenail; however, no evidence of relief of pain was presented in the data submitted for the combination product. The agency further notes that the Topical Analgesic Panel placed chlorobutanol in Category III for effectiveness as an external analgesic (December 4, 1979; 44 FR 69848). Further data are needed to demonstrate that the combination relieves pain, and to demonstrate the effectiveness of each active ingredient for its stated use.

Reference

(1) OTC Volume 160384.

C. Comments on Labeling of Ingrown Toenail Relief Drug Products

6. One comment contended that FDA does not have the authority to legislate the exact wording of OTC labeling claims to the exclusion of what the comment described as other equally truthful claims for the products. The comment objected to the labeling recommended by the Panel as being overly restrictive and recommended that more flexibility in labeling be permitted by adding the following statement to each subsection of §358.450 " * * * or similar statements which are in keeping with the Panel's report."

Since the inception of the OTC drug review, the agency has maintained that a monograph describing the conditions under which an OTC drug will be generally recognized as safe and effective and not misbranded must include both specific active ingredients and specific labeling. (This policy has become known as the "exclusivity rule.") The agency's position has been that it is necessary to limit the acceptable labeling language to that developed and approved through the OTC drug review process in order to ensure the proper and safe use of OTC drugs. The agency has never contended, however, that any list of terms developed during the course of the review literally exhausts all the possibilities of terms that appropriately can be used in OTC drug labeling. Suggestions for additional terms or for other labeling changes may be submitted as comments to proposed or tentative final monographs within the specified time periods or through petitions to amend monographs under 21 CFR 330.10(a)(12). For example, the labeling proposed in this tentative final monograph has been expanded and revised in response to comments received.

During the course of the review, FDA's position on the "exclusivity rule" has been questioned many times in comments and objections filed in response to particular proceedings and in correspondence with the agency. The agency has also been asked by the Proprietary Association to reconsider its position. To assist the agency in resolving this issue, FDA plans to conduct an open public forum on September 29, 1982 where all interested parties can present their views. The forum will be a legislative type administrative hearing under 21 CFR Part 15 that will be held in response to a request for a hearing on the tentative final monograph for nighttime sleep-aids (published in the **Federal Register** of June 13, 1976; 43 FR 25544). Details of the hearing were announced in a notice published in the **Federal Register** of July 2, 1982 (47 FR 29002). In proposed and tentative final monographs issued in the meantime, the agency will continue to state its longstanding policy. Accordingly, the agency at this time does not accept the comment's recommendation to add to the monograph the statement "* * * or similar statements which are in keeping with the Panel's report."

7. One comment suggested that the term "ingrown toenail relief drug product," recommended by the Panel as a statement of identity in § 358.450(a), not be used to describe this class of products because the wording is excessively cumbersome and not consistent with other previously proposed statements that present the intended activity in a more succinct manner. The terms "ingrown toenail treatment" and "ingrown toenail relief" were suggested as alternatives.

The agency believes that the term "ingrown toenail relief" is generally an allowable alternative for the term "ingrown toenail relief drug product" as it accurately describes the expected action of these products; however, this term should be modified to "ingrown toenail reliever" for grammatical precision. Section 358.450(a) will be modified to allow the use of this term as an alternative statement of identity. The agency is also proposing to shorten the Panel's recommended statement of identity, to make it less cumbersome, by deleting the word "drug."

The term "ingrown toenail treatment" does not describe the action of the product. "Treatment" is defined as the systematic effort to cure illness and relieve symptoms (Ref. 1). These products are indicated only for the temporary relief of discomfort from ingrown toenails, not as a cure for the condition. Accordingly, the agency is not proposing this term in the tentative final monograph.

Reference

(1) "The Random House College Dictionary," Random House, Inc., New York, 1980, s.v. "treatment."

8. One comment contended that the products reviewed by the Panel have a greater efficacy in the management of "incurvated nails," than of "ingrown nails" which have penetrated the skin and have provided a potential site for bacterial infection. The comment recommended that the indications for these products be changed accordingly.

OTC ingrown toenail products are intended to relieve the discomfort of embedded nails; they are not intended to be used on nails that have penetrated the skin and may result in an infection. As the Panel noted, the term "ingrown toenail" was described by Grinell (Ref. 1) as a misnomer, because the nail never grows into the flesh, but instead becomes embedded. The Panel stated that the labeling of a product intended to relieve discomfort of ingrown toenail should state the nature and use of the product in language that is clear and easy for a lay user to understand (45 FR 69130). Even though the term "incurvated toenail" may more accurately describe the condition for which these OTC drug products are intended, the agency believes that it is not apt to be as well understood by consumers. Therefore, the term "ingrown toenail" is being proposed in

the tentative final monograph because consumers are more familiar with this term, and it is accepted in general usage as meaning a toenail that has become embedded (ref. 2).

References

(1) Grinell, R. N., "Ingrown Toe Nail," *Podiatry Quarterly*, 2:8–10, 1964.

(2) "Webster's New Collegiate Dictionary," G. and C. Merriam Co., Springfield, MA, 1976, s. v. "ingrown."

9. One comment requested amending the Panel's recommended indications in § 358.450(b) to include the following: "relieves pain by softening callused tissue and embedded (ingrown) toenails" (for sodium sulfide only) and "helps relieve the pain, redness, and tenderness of ingrown toenails." The comment argued that these statements accurately present the indications for use for these products and should be allowed because the ingredients sodium sulfide and tannic acid provide the intended result by means of totally different mechanisms of action.

The agency does not find the phrase "relieves pain by softening callused tissue and embedded (ingrown) toenails" acceptable at this time as an indication for sodium sulfide. As discussed in comment 2 above and comment 10 below, the effectiveness of sodium sulfide as a nail softener and pain reliever has not been demonstrated. The agency will reserve judgment on this additional indication until sodium sulfide has been shown to be effective.

The Panel believed OTC ingrown toenail relief drug products should not be used if symptoms of infection were present. The Panel emphasized that infections are not amenable to self-treatment and that, if signs of infection appear, a doctor should be consulted immediately. The symptoms in the comment's suggested indication "helps relieve the pain, redness, and tenderness of ingrown toenails" are very similar to those of an infection, i.e., pain, redness, and swelling. The comment's proposed indication might lead to consumer confusion or misuse of the product and delay seeking professional treatment as needed. The agency concurs with the Panel and is not adopting the comment's suggested indication.

10. One comment requested deletion of the Panel's recommended warning in § 358.450(c)(2), "Do not use this product for more than 7 days," for products containing sodium sulfide. The comment contended that the mechanism of action of sodium sulfide involves a softening of the ingrown toenail and the surrounding callused tissue by reduction of disulfide cross-linkages, that this gradual process may require several weeks to provide maximal benefits, and that prolonged use in no way jeopardizes the safety of the person suffering from this painful condition. The comment stated that it is appropriate to warn the consumer to seek professional treatment if no improvement is noticed, but that the warnings should not include a 7-day limitation on use if relief is being obtained.

The comment also recommended combining the warnings in § 358.40(c)(2) and (4) to eliminate some of the duplicate wording. The revised warning would read "Consult your doctor or podiatrist if your condition worsens, if a discharge is present around the nail, if redness or swelling of the toe increases, or if no improvement is seen. Do not apply this product to open sores."

The Panel reviewed a clinical study on the effectiveness of sodium sulfide. According to the researchers conducting the study, moderate to complete relief of pain and tenderness due to ingrown toenails was noted within 3 to 7 days (Ref. 1). However, the Panel found several problems with the study and concluded that the results had to be corroborated, either by repeating it or by an additional study using a similar protocol. The comment did not submit any data to support the effectiveness of sodium sulfide or to show that several weeks may be required to obtain maximal benefits. Until data are submitted that demonstrate effectiveness and different timeframes within which sodium sulfide provides relief, the agency will retain the 7-day use limitation warning. As mentioned in comment 2 above, the agency proposes to leave sodium sulfide in Category III at this tentative final monograph stage.

The agency does not believe that the warnings in § 358.450(c)(2) and (4) should be combined. The intent of these warnings is to alert consumers to separate and distinct potential medical problems. The purpose of the warning in § 358.450(c)(2) "Do not use this product for more than 7 days. Consult a doctor if no improvement is seen after 7 days." is to inform consumers of the limitations of the usefulness of OTC ingrown toenail relief drug products. This warning is designed to assist the user in determining when the limits of self-treatment have been reached. Because doctors may recommend use of these products for a period exceeding 7 days, the agency is expanding the first sentence of the warning to read "Do not use this product for more than 7 days unless directed by a doctor."

The warning in § 358.450(c)(4) advises the consumer to discontinue use and to see a doctor if signs of an infection appear because infections are not amenable to self treatment. The agency believes that the warnings, as presently worded, are easier to understand and more meaningful to the consumer.

Reference

(1) OTC Volume 160280.

11. One comment requested changing the warning in § 358.450(c)(3) to read "If you have diabetes or circulatory impairment, see a doctor or podiatrist for treatment of ingrown toenail." The comment stated that podiatrists provide valuable professional treatment of various afflictions of the feet and, therefore, it is appropriate to direct the consumer to consult either a physician or a podiatrist in this instance.

The Panel considered this issue in its review of OTC corn and callous drug products and decided against using the term "podiatrist" in the labeling (Ref. 1). The Panel felt that the two terms were synonymous and concluded that the term "doctor" was sufficient; the agency concurs, believing that no one would rule out seeing a podiatrist on the grounds that the term was not specifically included in the warning. Therefore, the agency does not propose to change the wording of this warning in the tentative final monograph.

Reference

(1) Transcript of Proceedings of the Advisory Review on OTC Miscellaneous External Drug Products, April 20, 1980. p. 42.

12. One comment recommended substituting the term "poor circulation" for "circulatory impairment" in § 358.450(c)(3). The comment stated that the term "poor circulation" would be better understood by the lay consumer.

The agency concurs and is proposing that the warning be revised to read "If you have diabetes or poor circulation, see a doctor for treatment of ingrown toenail."

13. One comment contended that the "Directions" recommended by the Panel in § 358.450(d) are too brief and need to be clarified in two areas: (1) The consumer is not told whether to wet the cotton with the drug product before or after placing the cotton in the nailgroove, and (2) the consumer is not told whether to change the cotton several times daily when application of the product is repeated, or merely to apply the drug to the original, or previously-used, piece of cotton. The comment pointed out that the Panel did not refer to any research on the advisability of frequent changes of the cotton and suggested that this subject be examined prior to clarifying these parts of the directions.

The agency agrees with the comment that the Panel's recommended "Directions" in § 358.450(d) could be revised to make them clearer to consumers. The agency is not aware of studies designed to show that removing or reusing the cotton previously saturated with the drug product would adversely affect the treatment of ingrown toenails. The agency does not believe there is any reason why the drug could not be added to the same piece of cotton several times during the course of one day. However, the agency believes that the consumer should change the cotton at least once daily for hygienic reasons. Therefore, the agency is proposing to revise the appropriate portion of the directions to read: "* * * wet cotton thoroughly with the solution several times daily until nail discomfort is relieved. Change cotton at least once daily. Do not use product for more than 7 days unless directed by a doctor."

II. The Agency's Tentative Adoption of the Panel's Report

A. Summary of Ingredient Categories and Testing of Category II and Category III Conditions

1. *Summary of ingredient categories.* The Panel placed tannic acid and sodium sulfide in Category III because available data were insufficient to permit final classification. The Panel concluded that tannic acid is safe in concentrations up to 25 percent, but there are insufficient data available to determine its effectiveness as an ingrown toenail relief active ingredient. Although sodium sulfide in concentrations up to 1 percent was considered safe, there were insufficient data available to establish its effectiveness as an ingrown toenail relief active ingredient. FDA concurs with the Panel's classification of these ingredients.

For the convenience of the reader, the following table is included as a summary of the categorization of ingrown toenail relief active ingredients by the Panel and the proposed classification by the agency:

Ingrown toenail relief active ingredients	Panel	Agency
Chloroxylenol	II	II.
Sodium sulfide	III	III.
Tannic acid	III	III.
Urea	II	II.

2. *Testing of Category II and Category III conditions.* The Panel did not recommend any testing guidelines for ingrown toenail relief drug products. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any ingrown toenail relief ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the **Federal Register** of September 29, 1981 (46 FR 47740). This policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Changes in the Panel's Recommendations

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the Panel's report and recommended monograph with the changes described in FDA's responses to the comments above and with other changes described in the summary below. A summary of the changes made in the Panel's conclusions and recommendations follows.

(1) The agency has modified the statement of identity in § 358.450(a) by deleting the term "drug" from the phrase and has added "ingrown toenail reliever" as an alternative phrase. (See comment 7 above.)

(2) The agency has expanded the warning in § 358.450(c)(2) by adding the words "unless directed by a doctor." (See comment 10 above.)

(3) The agency has modified the warning in § 358.450(c)(3) by substituting "poor circulation" for "circulatory impairment." (See comment 12 above.)

(4) The agency has modified a portion of the directions in § 358.450(d) to read: ". . . wet cotton thoroughly with the solution several times daily until nail discomfort is relieved. Change cotton at least once daily. Do not use product for more than 7 days unless directed by a doctor." (See comment 13 above.)

(5) This proposal constitutes Subpart D of Part 358, not Subpart E as stated in the Panel's recommended monograph. Accordingly, all sections of the tentative final monograph are numbered as § 358.300 instead of § 358.400.

The agency has examined the economic consequences of this proposed rulemaking and has determined that it does not require either a Regulatory Impact Analysis, as specified in Executive Order 12291, or a Regulatory Flexibility Analysis, as defined in the Regulatory Flexibility Act (Pub. L. 96–354).

Specifically, ingrown toenail relief drug products may continue to be marketed while additional testing is being performed. If none of these ingredients is elevated to Category I status, then there will be no active ingredients to include in a final monograph, and these products will have to be removed from the market. If any of these ingredients is elevated to Category I status, some relabeling will be necessary because the agency has made some minor revisions in the Panel's recommended labeling. Manufacturers will have up to 12 months to revise their product labeling. In most cases, this will be done at the next printing so that minimal costs should be incurred. Thus, the impact of a final rule appears to be minimal whether or not the ingredients are elevated to Category I status. Therefore, the agency concludes that the proposed rule is not a major rule as defined in Executive Order 12291. Further, the agency certifies that the proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC ingrown toenail relief drug products. Types of impact may include, but are not limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC ingrown toenail relief drug products should be accompanied by appropriate documentation. Because the agency has not previously invited specific comment on the economic impact of the OTC drug review on ingrown toenail relief drug products, a period of 120 days from the date of publication of this proposed rulemaking in the **Federal Register** will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has carefully considered the potential environmental effects of this proposal and has concluded that the action will not have significant impact on the human environment and an environmental impact statement therefore will not be prepared. The agency's finding of no significant impact and the evidence supporting this finding, contained in an environmental assessment (under 21 CFR 25.31, proposed in the **Federal Register** of December 11, 1979; 44 FR 71742), may be seen in the Dockets Management Branch, Food and Drug Administration.

List of Subjects in 21 CFR Part 358

Over-the-counter drugs, Skin bleaching agents, Wart removers, Nailbiting and thumbsucking deterrents, Ingrown toenail relief.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 as revised (see 47 FR 16010; April 14, 1982), it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended in Part 358 by adding new Subpart D, to read as follows:

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

* * * * *

Subpart D—Ingrown Toenail Relief Drug Products

Sec.

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704).

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 of the conditions in this subpart in addition to each of the general conditions established in § 330.1.

(b) References in this subpart to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 358.303 Definition.

As used in this subpart:

Ingrown toenail relief drug product. A drug product applied to an ingrown toenail that will correct the condition either by softening the nail or by hardening the nail bed.

§ 358.310 Ingrown toenail relief active ingredients. [Reserved]

§ 358.350 Labeling of ingrown toenail relief drug products.

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

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the following: "For temporary relief of discomfort from ingrown toenails."

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

(1) "For external use only."

(2) "Do not use this product for more than 7 days unless directed by a doctor. Consult a doctor if no improvement is seen after 7 days."

(3) "If you have diabetes or poor circulation, see a doctor for treatment of ingrown toenail."

(4) "Do not apply this product to open sores. If redness and swelling of your toe increase, or if a discharge is present around the nail, stop using this product and see your doctor."

(d) *Direction.* The labeling of the product contains the following statement under the heading "Directions":

"Cleanse affected toes thoroughly. Place a small piece of cotton in the nail groove (the side of the nail where the pain is) and wet cotton thoroughly with the solution several times daily until nail discomfort is relieved. Change cotton at least once daily. Do not use product for more than 7 days unless directed by a doctor."

Interested persons may, on or before November 2, 1982, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before January 2, 1983. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests 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. Comments, objections, and requests may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register.**

Interested persons, on or before September 3, 1983, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before November 3, 1983. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA–305) (address above). Received data and comments may also be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on November 3, 1983. Data submitted after the closing of the adminstrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register** unless the Commissioner finds good cause has been shown that warrents earlier consideration.

Mark Novitch,

Acting Commissioner of Food and Drugs.

Dated: August 9, 1982.

Richard S. Schweiker,

Secretary of Health and Human Services.

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