(preferably in four copies and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal on or before January 14, 1981. Comments should be addressed to the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, and may be accompanied by a supporting memorandum or brief. Comments replaying to comments may also be submitted on or before February 16, 1981. Comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

In accordance with Executive Order 12044, as amended by Executive Order 12221, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of the regulatory analysis assessment supporting this determination is on file with the Hearing Clerk, Food and Drug Administration.

Dated: October 6, 1980.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 80–31958 Filed 10–15–80; 8:45 am]

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21 CFR Part 358

[Docket No. 80–0348]

Ingrown Toenail Relief Drug Products for Over-the-Counter Human Use; Establishment of a Monograph

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: This proposed rule would establish conditions under which over-the-counter (OTC) ingrown toenail relief drug products are generally recognized as safe and effective and not misbranded. The proposed rule, based on the recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products, is part of the ongoing review of OTC drug products conducted by the Food and Drug Administration (FDA).

DATES: Comments by January 14, 1981, and reply comments by February 16, 1981.

ADDRESS: Written comments to the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD–510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–4960.

SUPPLEMENTARY INFORMATION: In accordance with part 330 (21 CFR part 330), FDA received on April 21, 1980 a report on ingrown toenail relief drug products from the Advisory Review Panel on OTC Miscellaneous External Drug Products.

Under § 330.10(a)(6) (21 CFR 330.10(a)(6)), the agency issues (1) a proposed regulation containing the monograph recommended by the Panel, which establishes conditions under which OTC ingrown toenail relief drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel detemined that they would result in the drugs' not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's diliberations. The report has been prepared independently of FDA, and the agency has not yet fully evaluated the report. The Panel's findings appear in this document as a formal proposal to obtain public comment before the agency reaches any decision on the Panel's recommendations. This document represents the best scientific judgment of the Panel members but does not necessarily reflect the agency's position on any particular matter contained in it. After reviewing all comments submitted in respose to this proposal, FDA will issue a tentative final regulation in the **Federal Register** to establish a monograph for OTC ingrown toenail relief drug products.

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information concerning OTC ingrown toenail relief drug products submitted for consideration by the Advisory Review Panel. All the submitted information will be put on public display at the Hearing Clerk's Office, Food and Drug Administration, after November 17, 1980, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD–510) (address above).

Based upon the conclusions and recommendations of the Panel, FDA proposes the following:

1. That the conditions included in the monograph, under which the drug products would be generally recognized as safe and effective and not misbranded (monograph conditions), be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

2. That the conditions excluded from the monograph, either because they would cause the drug to be not generally recognized as safe and effective or to be misbranded or because the available data are insufficient to support the inclusion of such conditions in the monograph (nonmonograph conditions), be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the **Federal Register,** regardless of whether further testing is undertaken to justify their future use.

FDA published in the **Federal Register** of May 13, 1980 (45 FR 31422) its proposal to revise 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 regulations (21 CFR 330.10) are unlawful to the extent that they authorize the marketing of Category III drugs after a final monograph. Accordingly, the proposed regulations delete this provision and 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 (45 FR 31422).

Although it was not required to do so under *Cutler,* FDA has also decided to stop using 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). Any OTC drug product containing a "nonmonograph condition" will be subject to regulatory action after the establishment of a final monograph. This document, however, retains the concepts of Categories I, II, and III because that was the framework in

which the Panel conducted its evaluation of the data.

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was announced in the **Federal Register** of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the **Federal Register** of May 11, 1972 (37 FR 9464). In accordance with these regulations, requests for data and information on all active ingredients used in OTC miscellaneous external drug products were issued in the **Federal Register** of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179).

The Commissioner of Food and Drugs appointed the following Panel to review the information submitted and to prepare a report under § 330.10(a) (1) and (5) on the safety, effectiveness, and labeling of those products:

William E. Lotterhos, M.D., Chairman.
Rose Dagirmanjian, Ph. D.
Vincent J. Derbes, M.D. (resigned July 1976).
George C. Cypress, M.D. (resigned November 1978).
Yelva L. Lynfield, M.D. (appointed October 1977).
Harry E. Morton, Sc. D.
Marianne N. O'Donoghue, M.D.
Chester L. Rossi, D.P.M.
J. Robert Hewson, M.D. (appointed September 1978).

Representatives of consumer and industry interests served as nonvoting members of the Panel. Marvin M. Lipman, M.D., of Consumers Union served as the consumer liaison. Gavin Hildick-Smith, M.D., served as industry liaison from January until August 1975, followed by Bruce Semple, M.D., until February 1976. Both were nominated by the Proprietary Association. Saul A. Bell, Pharm. D., nominated by the Cosmetic, Toiletry, and Fragrance Association, also served as an industry liaison since June 1975.

Two nonvoting consultants, Albert A. Belmonte, Ph. D., and Jon J. Tanja, R.Ph., M.S., have provided assistance to the Panel since February 1977.

The following FDA employees assisted the Panel: John M. Davitt served as Executive Secretary until August 1977, followed by Arthur Auer until September 1978, followed by John T. McElroy, J.D., Thomas D. DeCillis, R.Ph., served as Panel Administrator until April 1976, followed by Michael D. Kennedy until January 1978, followed by John T. McElroy, J.D., Joseph Hussion, R.Ph., served as Drug Information Analyst until April 1976, followed by Victor H. Lindmark, Pharm. D., until March 1978, followed by Thomas J. McGinnis, R.Ph.

The Advisory Review Panel on OTC Miscellaneous External Drug Products was charged with the review of many categories of drugs. Due to the large number of ingredients and varied labeling claims, the Panel decided to review and publish its findings separately for several drug categories and individual drug products. The Panel presents its conclusions and recommendations for ingrown toenail relief drug products in this document. The review of other categories of miscellaneous external drug products will be continued by the Panel, and its findings will be published periodically in future issues of the **Federal Register.**

The Panel was first convened on January 13, 1975 in an organizational meeting. Working meetings which dealt with the topic in this document were held on: May 16 and 17, 1976; August 5 and 6, September 30, October 1, December 11 and 12, 1977; April 16 and 17, June 11 and 12, May 18 and 19, August 3 and 4, September 28 and 29, October 28 and 29, and December 9 and 10, 1979; January 27 and 28, March 7 and 8, and April 20 and 21, 1980.

The minutes of the Panel meetings are on public display in the Hearing Clerk's Office (HFA-305), Food and Drug Administration (address above).

The following individuals were given an opportunity to appear before the Panel, either at their own request or at the request of the Panel, to express their views on ingrown toenail relief drug products:

Barry Brooks, J.D.
Joel Hertz, Ph. D.

No person who so requested was denied an opportunity to appear before the Panel.

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from interested persons, and has considered all pertinent information submitted through April 21, 1980 in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations in § 330.10, the Panel reviewed OTC ingrown toenail relief drug products with respect to the following three categories:

Category I. Conditions under which OTC ingrown toenail relief drug products are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC ingrown toenail relief drug products are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

I. Submission of Data and Information

In an attempt to make this review as extensive as possible and to aid manufacturers and other interested persons, the agency compiled a list of ingredients recognized, either through historical use or use in marketed products, as ingrown toenail relief active ingredients. Six ingredients were identified as follows: benzocaine, dibucaine, isopropyl alcohol, para-chloro-metaxylenol, sodium sulfide, and tannic acid. Notices were published in the **Federal Register** of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179) requesting the submission of data and information on these ingredients or any other ingredients used in OTC ingrown toenail relief drug products.

A. Submissions

Pursuant to the above notices, the following submissions were received:

Firms and Marketed Products

Scholl, Inc., Chicago, IL 60610—Onixol.
Whitehall Laboratories, Inc., New York, NY 10017—Outgro.

B. Ingredients Reviewed by the Panel

1. *Labeled ingredients contained in marketed products submitted to the Panel.*

Chlorobutanol
Isopropyl alcohol
Sodium sulfide
Tannic acid

2. *Other ingredients reviewed by the Panel.*

Benzocaine
Dibucaine
Para-chloro-metaxylenol
Triethanolamine
Urea

C. Classification of Ingredients

1. *Active ingredients.*

Sodium sulfide
Tannic acid

2. *Inactive ingredients.*

Isopropyl alcohol
Triethanolamine

3. *Ingredients reviewed by other Panels.* The following ingredients have previously been classified by the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products in the **Federal Register** of December 4, 1979 (44 FR 69768).

Benzocaine
Chlorobutanol
Dibucaine

4. *Other ingredients.* The Panel was not able to locate nor is it aware of data demonstrating the safety and

effectiveness of the following ingredients when used as OTC ingrown toenail relief active ingredients. The Panel, therefore, classifies these ingredients as Category II for this use, and they will not be discussed further in this document.

Chloroxylenol (para-chloro-metaxylenol)
Urea

D. Referenced OTC Volumes

The "OTC Volumes" cited throughout this document include submissions made by interested persons in response 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). All the information included in these volumes, except for those deletions which are made in accordance with confidentiality provisions as set forth in § 330.10(a)(2), will be put on public display after November 17, 1980, in the Hearing Clerk's Office (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rochville, MD 20857.

II. General Discussion

Nails serve as a means of protection for the upper ends of the toes. The flattened, expanded, free end of the nail protects the softer tissue of the end of the toe. The ingrown toenail (onychocryptosis) is a condition in which the side of the nail becomes imbedded in the surrounding soft tissue of the toe and causes pain. Secondary complications that can arise from the ingrown toenail condition are simple inflammation, swelling, ulceration, cellulitis (wide-spread inflammation of tissue), granulation tissue (rounded masses), infection, lymphangitis (red streaks on foot and leg), and septicemia (blood poisoning).

Grinnell (Ref. 1) describes the term ingrown toenail as a misnomer, because the nail never grows into the flesh but instead becomes imbedded. The correct method of cutting the toenail to prevent an ingrown toenail is to cut the nail straight across without tapering the corners in any way. The cause of most ingrown toenail conditions is incorrect cutting of the toenail but may also result from injury to the matrix or from hereditary tendencies. Acute symptoms of an ingrown toenail do not necessarily develop immediately after incorrect cutting; usually several days elapse before irritation becomes evident. Short and tight hosiery or tight shoes can also cause ingrown toenail, since improper footwear can force the lateral edge of the nail into the softer tissues by direct pressure. Tight bed covers, creating pressure of the soft skin tissue against the nails, can cause bed-ridden patients to have ingrown toenails (Ref. 1). Fungus infection of the nails (onychomycosis) may sometimes cause the nails to thicken and develop ragged edges. The movement of walking can cause these nail edges to irritate and penetrate the grooves on both sides of the toenail. In some families there is a tendency toward curling of the toenails; individuals in these families are predisposed to developing ingrown nails.

In treating a case of ingrown toenail in its early stages before the surrounding tissue of the nail has become enlarged, considerations are hardening of the nail groove and shrinking the soft tissue, so that there will be sufficient room for the nail to resume its normal position adjacent to the soft tissue. Prevention of infection is also a consideration at this time.

Reference

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

General Labeling

The Panel has reviewed the general labeling requirements previously adopted by the Food and Drug Administration for OTC products (21 CFR 201.60, 201.61, and 201.62) and agrees that these general requirements are appropriate for labeling of products intended to relieve the symptoms of ingrown toenail.

1. *Indications and directions for use.* The Panel believes 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 and should provide the user with enough information for safe and effective use of the product.

No reference should be made or implied regarding the relief of symptoms unrelated to the condition that is an indication for use of the product.

2. *Warnings against unsafe use.* Because the ingredients in products intended to provide relief from discomfort of ingrown toenail might be toxic if absorbed through broken skin, of at least excessively irritating, the Panel recommends a label warning against application of these products to open sores. Labeling should also specify that these products are for external use only.

A statement of the maximum length of time the products should be used for self-treatment should be included in labeling, as well as a warning to consult a doctor if symptoms of infection, such as redness and swelling or discharge around the nail, should occur. The Panel believes that infection is not amenable to self-treatment, that self-treatment of infection might in fact permit it to progress to a serious stage, and that, if signs of infection appear, a doctor should be consulted immediately.

The Panel is also concerned about the use of these products by diabetics and persons having impaired circulation to the feet. These individuals are susceptible to infection and can have numbing of sensation in the feet which might mask the pain of an infected ingrown toenail. The Panel therefore recommends that the labeling of products intended to provide relief from the discomfort of ingrown toenail contain a warning to diabetics and persons having circulatory impairment to see a doctor for treatment of this condition.

III. Categorization of Data

A. Category I Conditions

These are conditions under which active ingredients used for ingrown toenail relief are generally recognized as safe and effective and are not misbranded. The Panel recommends that Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

1. *Category I ingredients.* None.

2. *Category I labeling.* The Panel recommends the following labeling for Category I drug products to relieve symptoms of ingrown toenail.

a. *Indications.* "For temporary relief of discomfort from ingrown toenails."

b. *Warnings.* (1) "For external use only."

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

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

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

c. *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. Repeat several times daily until nail discomfort is relieved, but do not use for more than 7 days."

B. Category II Conditions

These are conditions under which active ingredients used for ingrown toenail relief are not generally recognized as safe and effective or are misbranded. The Panel recommends that the Category II conditions be

eliminated from OTC ingrown toenail relief drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

1. *Category II ingredients.* See part I. paragraph C.4. above—Other ingredients.

2. *Category II labeling.* The Panel has placed in Category II the following labeling claim: "For fast pain relief."

C. Category III Conditions

These are conditions for which available data are insufficient to permit final classification at this time.

1. *Category III ingredients.*

Sodium sulfide
Tannic acid

a. *Sodium sulfide.* The rationale for the use of sodium sulfide in treating ingrown toenail discomfort is that this ingredient softens the keratin in the nail and the calloused skin surrounding the nail, thereby providing relief from pressure and pain caused by contact of the imbedded nail with the skin.

The Panel concludes that sodium sulfide is safe for this use as applied according to the dosage and directions specified below, but there are insufficient data available to determine its effectiveness.

(1) *Safety.* Sodium sulfide has been shown to have an intraperitoneal lethal dose (LD_{50}) in mice of 53 milligrams per kilogram (mg/kg) (Ref. 1). A marketed OTC product containing 1 percent sodium sulfide has been subjected to acute toxicity studies in young albino rats and the acute oral LD_{50} was determined to be 25.5 grams per kilogram (G/KG) (ref. 1). The oral LD_{50} for a 70-gram human is 50 to 500 MG/KG (ref. 2).

Necropsy revealed gastrointestinal tract hemorrhaging, pale livers, pale kidneys, and mottled lungs. No gross pathologic alterations were noted among any of the animals sacrificed at the end of the 14-day observation period. Calculations based on results of this study show that a 70-kg human would need to consume more than 1 quart of a 1-percent sodium sulfide preparation to achieve a lethal dose.

In assessing the irritancy of sodium sulfide, a 1-percent preparation was tested for eye irritation in young albino rabbits. The preparation was classified as minimally irritating based on irritation and damage to the cornea, iris, and conjuntiva (Ref. 2).

(2) *Effectiveness.* Nail keratin is very similar in structure and composition to hair keratin (Ref. 3), and chemicals that soften hair keratin may be useful in softening nail keratin. Sodiium sulfide was used as a hair depilatory as early as 1893, and this ingredient is the basis of most liquid depilatories (Refs. 1 and 4).

A solution of 1 percent sodium sulfide in a water and emollient vehicle was evaluated for effectiveness as a nail softener in a double-blind study conducted on 100 subjects with ingrown toenail problems. Fifty subjects were treated with the 1-percent sodium sulfide preparation, and 50 subjects were treated with the vehicle alone as a control. Initial treatment with the test and control solutions was conducted by clinicians who were directed to cleanse each affected toe thoroughly and place a small piece of cotton in the nail groove. The cotton was then saturated with the respective solutions. Subsequent treatment was done by the subjects according to directions from the clinicians, and treatments were repeated three times per day for a maximum of 7 days unless pain was relieved earlier. The subjects returned for examination on the third and seventh days of the study.

According to the researchers conducing the study, moderate to complete relief of pain and tenderness due to ingrown toenails was noted within 3 to 7 days with the use of the sodium sulfide preparation, while little or no relief of pain was noted with the vehicle alone (Ref. 2).

However, careful analysis of this study reveals several problems. Subjects were to be placed by each investigator into respective groups in equal numbers, according to age, sex, and duration and severity of the pain. This protocol was not followed, and the randomization of patient population and assignment of treatment was defective. Although the protocol specified a double-blind study, the actual test conditions did not meet double-blind test conditions. The subject report form containing the rating systems to be used by the clinicians was revised by several investigators. Thus comparisons and statistical treatment of the results could not be done accurately.

A total of 10 investigators were to be utilized in the study. Two investigators, however, did not conduct any studies, while a third investigator reported data, but no background information or credentials were submitted for him. One subject-report form had an investigator's signature which differed from all the others he had signed.

Thus, the Panel has concluded that, in order to establish the effectiveness of sodium sulfide as an ingrown toenail relief softener, it is necessary for the results of this study to be corroborated, either by additional study or by repetition of this study using a similar protocol.

(3) *Proposed dosage.* Topical dosage is a 1-percent solution of sodium sulfide in a suitable vehicle.

(4) *Labeling.* The Panel recommends Category I labeling for active ingredients to relieve the symptoms of ingrown toenail. (See part III. paragraph A.2. above—Category I labeling.)

References

(1) OTC Volume 160100.
(2) OTC Volume 160280.
(3) Baden, H. P., "The Physical Properties of Nail," *The Journal of Investigative Dermatology,* 55:115–122, 1970.
(4) Wells, F. V., and I. Lubowe, "Cosmetics and the Skin," Reinhold Publishing Corp., New York, pp. 363–364, 1964.

b. *Tannic acid.* Tannic acid is a tannin usually obtained from nutgalls, which are excessive growths formed on young twigs of certain oak trees as a result of development of eggs deposited by the female gall fly. Tannic acid occurs as an amorphous powder, glistening scales, or spongy masses, yellowish-white to light brown in color. Tannic acid has a faint, characteristic odor and strong astringent taste; it is soluble in water and alcohol and almost insoluble in chloroform and ether (Ref. 1).

Tannic acid is classified as an astringent, that is, a substance that precipitates protein and thereby has such actions as hardening skin, forming a protective coating over mucous membranes, checking excessive secretion, and stopping superficial hemorrhage. It has been used therapeutically for all these actions (Ref. 1).

The claimed rationale for use of tannic acid in treating ingrown toenail is that it hardens the skin surrounding the imbedded nail and shrinks the soft tissue adjacent to the nail, making sufficient room for the nail to resume its normal position adjacent to the soft tissue.

(1) *Safety.* Tannic acid was formerly used orally for the symptomatic treatment of diarrhea, topically for the management of extensive burns, and rectally for the relief of various rectal disorders (Ref. 2). However, these applications are now practically obsolete because sufficient tannic acid may be absorbed from the gastrointestinal tract, denuded surfaces, and mucous membranes to cause severe damage to the liver (Refs. 3 through 5). In 1942, Wells et al. (Ref. 3) reported that treatment of severe burns with tannic acid resulted in toxic hepatitis within 36 hours.

The Panel notes that the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment

Drug Products, in reviewing tannic acid as a skin protectant and burn treatment agent, concluded that tannic acid has little action on intact skin (43 FR 34644). This view supports the safety of tannic acid when applied to a small area of intact skin, such as that surrounding an ingrown toenail, and the Advisory Review Panel on OTC Miscellaneous External Drug Products concludes that tannic acid is safe when so applied in concentrations up to 25 percent.

(2) *Effectiveness.* The Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products noted that tannic acid has little action on intact skin. This casts doubt on the effectiveness of tannic acid when used to harden the skin and shrink the tissue surrounding an ingrown toenail.

The Advisory Review Panel on OTC Miscellaneous External Drug Products is aware of several studies dealing with tannic acid. One uncontrolled study by Grinnell (Ref. 6) deals with the effectiveness of tannic acid in treating ingrown toenail relief. He studied the effects of a product combining 25 percent tannic acid, 5 percent chlorobutanol, a topical anesthetic, and 69.25 percent isopropyl alcohol, an antiseptic, on 44 patients suffering from ingrown toenails. The patients were instructed to apply several drops of the medication in the crevice where the nail was imbedded in the flesh, to work the medication under the nail, let it dry thoroughly without rubbing it off, and to repeat this procedure several times a day. Forty of the 44 patients were professionally reevaluated 5 hours to 9 days after initial application of the medication. The other four patients telephoned in their own evaluations. According to Grinnell, the product proved to be an excellent aid in helping to restore the nail to its proper relationship to the soft tissue of the toe, and 94 percent of the patients who experienced swelling in connection with an ingrown toenail obtained complete relief from the swelling.

The Panel notes that it is not clear whether the swelling in these instances resulted from infection at the ingrown toenail site. If infection was initially present, then relief from swelling would very likely be the result of the germicidal activity of the isopropyl alcohol rather than the tissue-shrinking and skin-hardening activity of the tannic acid.

Another study (Ref. 7) tested the epidermal hardening of several ingredients in a combination product by preparing five nonabraded sites on albino rabbits for exposure to each of the following solutions: (a) untreated control, (b) 5 percent chlorobutanol in isopropyl alcohol, (c) 25 percent tannic acid in isopropyl alcohol, (d) 25 percent tannic acid and 5 percent chlorobutanol in isopropyl alcohol, and (e) isopropyl alcohol. Each site was treated topically once daily for 3, 7, and 10 days. The study concluded that the combination of 25 percent tannic acid and 5 percent chlorobutanol in isopropyl alcohol resulted in the greater skin thickening observed. However, the Panel concludes that this skin thickening cannot be equated to a skin-hardening effect.

Further studies were undertaken to demonstrate skin hardening by (a) the measurement of the resistance of treated and untreated excised mouse skin to a sharp needle dropped from a measured distance above the skin, and (b) by determining the compressibility of treated and untreated excised mouse skin (Ref. 7). From the needle-pierce method it was concluded that the combination product, 25 percent tannic acid and 5 percent chlorobutanol in isopropyl alcohol, hardened or toughened the mouse skin as measured by resistance to needle penetration. From the compressibility method it was concluded, because treated mouse skin was less compressible than the untreated skin, that the hardness of mouse skin increased.

The Panel concludes that there is insufficient evidence to show that tannic acid alone is effective in hardening the skin and shrinking the soft tissue surrounding an ingrown toenail in humans. It is necessary for controlled studies to be done showing the effect of tannic acid alone on the intact skin and soft tissue surrounding an ingrown toenail.

(3) *Proposed dosage.* Topical dosage is tannic acid in concentrations up to 25 percent.

(4) *Labeling.* The Panel recommends Category I labeling for active ingredients to relieve the symptoms of ingrown toenail. (See part III. paragraph A.2 above—Category I labeling.)

References

(1) Osol, A., and R. Pratt, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 1140, 1973.

(2) Swinyard, E. A., "Surface-Acting Drugs," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, MacMillan Publishing Co., Inc., New York, p. 951, 1975.

(3) Wells, D. B., H. D. Humphrey, and J. J. Coll, "Relation of Tannic Acid to Liver Necrosis, Occurring in Burns," *New England Journal of Medicine,* 226:629–636, 1942.

(4) Barnes, J. M., and R. J. Rossiter, "Toxicity of Tannic Acid," *Lancet,* 2:218–222, 1943.

(5) Krezanoski, J. Z., "Tannic Acid: Chemistry, Analysis, and Toxicology," *Radiology,* 87:655–657, 1966.

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

(7) OTC Volume 160384.

2. *Category III labeling.* None.

D. Combination Policy

The Panel was not aware of any product combining OTC ingredients that it reviewed for relief of the symptoms of ingrown toenail. A combination that can soften the nail and harden the nailbed would be rational. Any combination of ingredients reviewed in this document with ingredients from other therapeutic categories should meet the criteria outlined in § 330.10(a)(4)(iv) which states:

> An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

In addition to the regulation cited above, the Panel concurs with the FDA's general guidelines for OTC drug combination products referred to in the **Federal Register** of November 28, 1978 (43 FR 55466). These guidelines provide for combining ingredients from different therapeutic categories and are thus applicable to combinations of ingredients for relief of the symptoms of an ingrown toenail with ingredients from other therapeutic categories.

> Category I active ingredients from different therapeutic categories may be combined to treat different symptoms concurrently *only* if each ingredient is present within its established safe and effective dosage range and the combination meets the OTC combination policy in all other respects.

The agency has determined that under 21 CFR 25.24(d)(9) (proposed in the **Federal Register** of December 11, 1979; 44 FR 71742) this proposal is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 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 authority delegated to the Commissioner (21 CFR 5.1), it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended by adding to Part 358, new Subpart E, to read as follows:

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

Subpart D—[Reserved]

Subpart E—Ingrown Toenail Relief Drug Products

Authority: Secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat 919 and 72 Stat 948 (21 U.S.C. 321, 352, 355, 371); (5 U.S.C. 553, 554, 702, 703, 704).

Subpart E—Ingrown Toenail Relief Drug Products

§ 358.401 Scope.

(a) An over-the-counter ingrown toenail relief drug product is a form suitable for topical application 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 I of Title 21 unless otherwise noted.

§ 358.403 Definitions.

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.

§ 358.410 Ingrown toenail relief active ingredients [Reserved].

§ 358.450 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 drug product."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the phrase "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. Consult a doctor if no improvement is seen after 7 days."

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

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

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions," followed by "or as directed by a doctor": "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. Repeat several times daily until nail discomfort is relieved, but do not use for more than 7 days."

Interested persons are invited to submit their comments in writing (preferably in four copies and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal on or before January 14, 1981. Comments should be addressed to the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, and may be accompanied by a supporting memorandum or brief. Comments replying to comments may also be submitted on or before February 16, 1981. Comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

In accordance with Executive Order 12044, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of the regulatory analysis assessment supporting this determination is on file with the Hearing Clerk, Food and Drug Administration.

Dated: October 6, 1980.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

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