DEPARTMENT OF HEALTH AND HUMAN SERVICES

21 CFR Part 358

[Docket No. 81N-0122]

Corn and Callus Remover Drug Products for Over-the-Counter Human Use; Establishment of a Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing an advance notice of a proposed rulemaking that would establish conditions under which over-the-counter (OTC) corn and callus remover drug products are generally recognized as safe and effective and not misbranded. This notice is based on the recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments by April 5, 1982, and reply comments by May 5, 1982.

ADDRESS: Written comments to the Dockets Management Branch (formerly the Hearing Clerk's Office) (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 June 22, 1980 a report on OTC corn and callus remover drug products from the Advisory Review Panel on OTC Miscellaneous External Drug Products. FDA regulations (21 CFR 330.10(a)(6)) provide that the agency issue in the **Federal Register** a proposed order containing: (1) The monograph recommended by the Panel, which establishes conditions under which OTC corn and callus remover drug products are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined 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 deliberations. 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 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 response to this document, FDA will issue in the **Federal Register** a tentative final monograph for OTC corn and callus remover drug products as a notice of proposed rulemaking. Under the OTC drug review procedures, the agency's position and proposal are first stated in the tentative final monograph, which has the status of a proposed rule. Final agency action occurs in the final monograph, which has the status of a final rule.

The agency's position on OTC corn and callus remover drug products will be stated initially when the tentative final monograph is published in the **Federal Register** as a notice of proposed rulemaking. In that notice of proposed rulemaking, the agency also will announce its initial determination whether the proposed rule is a major rule under Executive Order 12291 and will consider the requirements of the Regulatory Flexibility Act (5 U.S.C. 601-612). The present notice is referred to as an advance notice of proposed rulemaking to reflect its actual status and to clarify that the requirements of the Executive Order and the Regulatory Flexibility Act will be considered when the notice of proposed rulemaking is published. At that time FDA also will consider whether the proposed rule has a significant impact on the human environment under 21 CFR Part 25 (proposed in the **Federal Register** of December 11, 1979, 44 FR 71742).

The agency invites public comment regarding any impact that this rulemaking would have on OTC corn and callus remover drug products. Types of impact may include, but are not limited to, the following: Increased costs due to relabeling, repackaging, or reformulating; removal of unsafe or ineffective products from the OTC market; and testing, if any. Comments regarding the impact of this rulemaking on OTC corn and callus remover drug products should be accompanied by appropriate documentation.

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information concerning OTC corn and callus remover drug products submitted for consideration by the Panel. All the submitted information will be put on public display in the Dockets Management Branch, Food and Drug Administration, after February 4, 1982, except to the extent that the person submitting it demonstrates that it 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).

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.

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 because that was the framework in which the Panel conducted its evaluation of the data.

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 6 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 which 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. Further, any OTC drug products subject to this monograph which 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 voluntarily comply with the monograph at the earliest possible date.

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). (In making their categorizations with respect to "active" and "inactive" ingredients, the advisory review panels relied on their expertise and understanding of these terms. FDA has defined "active ingredient" in its current good manufacturing practice regulations (§ 210.3(b)(7), (21 CFR 210.3(b)(7))), as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." An "inactive ingredient" is defined in § 210.3(b)(8) as "any component other than an 'active ingredient,' ") In the **Federal Register** of August 27, 1975 (40 FR 38179), a notice supplemented the original notice with a detailed, but not necessarily all-inclusive, list of ingredients in miscellaneous external drug products. This list, which included ingredients for corn and callus removers, was provided to give guidance on the kinds of active ingredients for which data should be submitted. The notices of November 16, 1973, and August 27, 1975, informed OTC drug product manufacturers of their opportunity to submit data to the review at that time and of the applicability of the monographs from the OTC drug review to all OTC drug products.

Under § 330.10(a) (1) and (5), the Commissioner of Food and Drugs appointed the following Panel to review the information submitted and to prepare a report on the safety, effectiveness, and labeling of the active ingredients in these miscellaneous external drug 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 1976)
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 1978. 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 liason 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 Janaury 1978, followed by John T. McElroy, J.D. Joseph Hussion, R.Ph., seved 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 corn and callus remover drug products in this document. The findings of the Panel with respect to other categories of miscellaneous external drug products are being published periodically in 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: April 20 and 21, 1975, April 2 and 3, 1976; August 5 and 6, September 30, October 1, December 11 and 12, 1977; April 16 and 17, June 11 and 12, August 11 and 12, September 30, October 1, December 11 and 12, 1978; September 28 and 29, October 28 and 29, December 9 and 10, 1979; January 27 and 28, March 7 and 8, April 20 and 21, and June 22 and 23, 1980.

The minutes of the Panel meetings are on public display in the Dockets Management Branch (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 corn and callus remover drug products:

Robert Blank, Ph. D.
Phillip Brachman, D.P.M.
Barry Brooks, J.D.
Frank Dunlap, M.D.
Donald Hartung
Adam Kara, D.P.M.
Herbert Lapidus, Ph. D.
William Mueller
Mark Taylor

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 June 23, 1980 in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations in § 330.10, the Panel reviewed OTC corn and callus remover drug products with respect to the following three categories:

Category I. Conditions under which OTC corn and callus remover drug products are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC corn and callus remover 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.

The Panel reviewed 16 active ingredients in corn and callus remover drug products and classified 1 ingredient

in Category I, 13 ingredients in Category II, and 2 ingredients in Category III.

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 corn and callus remover active ingredients. Twenty-nine ingredients were identified as follows: Alkaloids of belladonna, allantoin (5-ureidohydantoin), ascorbic acid, beeswax, benzocaine, camphor gum, castile soap, castor oil, chlorobutanol, chlorophyll, collodion, cotton seed oil, ether, glacial acetic acid, ichthyol, iodine, lard, menthol, methylbenzethonium chloride, methyl salicylate, oil of eucalyptus, panthenol, pyroxylin, salol (phenyl salicylate), sodium carbonate, thymol, turpentine, vitamin A, and zinc chloride. 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 corn pads, plasters, and remedies, henceforth referred to as OTC corn and callous remover drug products.

A. Submissions

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

Firms and Marketed products

Chattem Drug & Chemical Co., Chattanooga, TN 37409—Blis-To-Sol.

Combe, Inc., White Plains, NY 10604—Blue Jay Corn Plasters.

E. G. Behren, Jackson, MI 49202—Corn/Callous Remover.

Scholl, Inc., Chicago, IL 60610—Callous Salve, Corn Salve, "2" Drop Corn/Callous Remover, Fixo Corn Plasters, Pink Medicated Disks for Corn Removal, Kurotex Corn Pads, Waterproof Corn Pads, Waterproof Small Corn Pads, Waterproof Callous Pads, Plastic Film Corn Pads, Pink Medicated Disks For Callous Removal, Medicated Disks for use with Zino Pads for Removing Soft Corns, Medicated Disks for use with Zino Pads for Removing Corns, Medicated Disks for use with Zino Pads for Removing Callouses, Presto Callous Pads, Presto Soft Corn Pads, Presto Corn Pads, Presto Small Corn Pads, Zino Small Corn Pads, Zino Corn Pads, Zino Callous Pads, Zino Soft Corn Pads.

Whitehall Laboratories, New York, NY 10017—Freezone.

B. Ingredients Reviewed by the Panel

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

Alcohol
Camphor
Castor oil
Diperodon hydrochloride
Ether
Oil of eucalyptus
Phenoxyacetic acid
Pyroxylin
Salicylic acid
Starch
Zinc chloride

2. *Other ingredients reviewed by the Panel.*

Alkaloids of belladonna
Allantoin (5-ureidohydantoin)
Ascorbic acid
Beeswax
Benzocaine
Camphor gum
Castile soap
Chlorobutanol
Chlorophyll
Collodion
Cotton seed oil
Glacial acetic acid
Ichthyol (ichthammol)
Iodine
Lard
Menthol
Methylbenzethonium chloride
Methyl salicylate
Panthenol
Salol (phenyl salicylate)
Sodium carbonate
Thymol
Turpentine
Vitamin A

C. Classification of Ingredients

1. *Active ingredients.*

Phenoxyacetic acid
Salicylic acid
Zinc chloride

2. *Inactive ingredients.*

Alcohol
Beeswax
Benzocaine
Camphor
Camphor gum
Castile soap
Castor oil
Chlorophyll
Collodion
Cotton seed oil
Ether
Eucalyptus oil (oil of eucalyptus)
Lard
Menthol
Pyroxylin
Sodium carbonate
Starch
Thymol
Turpentine

3. *Other ingredients.* The Panel was not able to locate nor is it aware of any data demonstrating the safety and effectiveness of the following ingredients when used as OTC corn and callus remover active ingredients. The Panel, therefore, classifies these ingredients as Category II for this use, and they will not be discussed further in this document.

Acetic acid, glacial (glacial acetic acid)
Allantoin (5-ureidohydantoin)
Ascorbic acid
Belladonna (extract) (alkaloids of belladonna)
Chlorobutanol
Diperodon hydrochloride
Ichthammol (ichthyol)
Iodine
Methylbenzethonium chloride
Methyl salicylate
Panthenol
Phenyl salicylate (salol)
Vitamin A

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 of the information included in these volumes, except for those deletions which are made in accordance with confidentiality provisions set forth in § 330.10(a)(2), will be put on public display after February 4, 1982, in the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

II. General Discussion

In normal skin the cells in the stratum basale epidermidis (bottom layer of the epidermis) undergo mitotic division (cell reproduction) followed by the migration of maturing cells through the stratum spinosum (prickle cell layer) and the stratum granulosum (granular layer of the epidermis). The migration rate is equal to the continual surface shedding of these cells. Normal mitotic activity and subsequent shedding lead to complete replacement of epidermis in about 1 month. In the case of a callus, friction and pressure against the surface of the skin increase the shedding rate which leads to a faster mitotic activity of the basal cell layer. This increased activity in turn produces a thicker stratum corneum (outermost layer) as more cells reach the outer surface of the skin. When the friction or pressure is relieved, the mitotic activity returns to normal, causing remission and disappearance of the callus (Ref. *1*).

A corn and callus are similar in that each has a marked thickening (hyperkeratosis) of the top layer of the skin. Both corns and calluses are caused by long periods of pressure or friction against the skin, and the affected areas respond with a thickening of the skin which is sometimes painful. It is usually when the affected area becomes painful that advice and consultation are sought or an OTC product is purchased.

A callus is a thickening of the skin having no central core, as opposed to a corn which has a definite core (Refs. *2* and *3*). A callus has indefinite borders and ranges from a few millimeters to several centimeters in diameter. A callus is usually raised, off-white, and has a normal pattern of skin ridges on its surface. Calluses form on weight-bearing areas in addition to the skin covering joints (e.g., on the palms of the hands, the sides and soles of the feet). Calluses also provide protection. Because the callus does protect, a reduction of the callus should be cautiously attempted, and the shoe, stocking, or other irritant cause should be removed (Ref. *4*).

In a reference submitted to the Panel, all hyperkeratolytic lesions studied on the plantar (bottom) surface of the foot and on either side of the large toe were classified as calluses (Ref. *5*). All lesions occurring on any surface of a toe, except on the sides of the large toe, were called corns.

Corns can be hard or soft and are usually associated with an underlying bony prominence, which causes a thickening, and a more compact central core, which is usually painful. According to Popovich (Ref. *1*), a corn is a raised, yellowish-gray thickening and ranges from a few millimeters to one or more centimeters in diameter. The base of the corn is on the surface of the skin; the apex points inward and presses nerve endings in the skin, causing pain (Ref. *1*).

Hard corns are the most common form of corns and occur on the surfaces of the toe joints (Ref. *6*). They are shiny and polished (Ref. *1*).

Soft corns are whitish thickenings of the skin that are usually found on the webs between the fourth and fifth toes and are continually macerated by accumulated sweat.

An intermediate between hard and soft corns is the so-called "O-corn" which is hard-rimmed, soft in the center, and usually very painful (Ref. *4*).

Seed corns are tiny compact areas within calloused skin on the sole of the foot, particularly in the metatarsal area, and usually are without symptoms (Ref. *4*).

A neurovascular corn has a highly vascular core (i.e., contains a large amount of blood), is not responsive to treatment, may occasionally bleed, and usually develops along the side of the foot near the big toe (Ref. *4*).

The Panel recommends that OTC corn and callus remover drug products be used only on calluses and hard corns. For the treatment of corns other than those described as hard, the Panel recommends that a doctor be consulted.

Corns generally arise from poorly fitting shoes, improperly fitted hosiery, or orthopedic problems (Ref. *5*). Orthopedic problems include improper weight distribution, pressure, and the development of bunions (a swelling over the area of the ball of the great toe, with thickening of the overlying skin and the forcing of this toe toward the little toe) (Ref. *1*). Other conditions occurring on the feet, such as warts or tumors, may be mistaken for corns or calluses. The Panel, therefore, recommends that hyperkeratotic foot lesions which persist despite self-treatment should be evaluated by a doctor.

The Panel further recommends that OTC drug preparations for removing corns and calluses should not be used by diabetics and persons with poor circulation except on the advice and under the supervision of a doctor. These persons are more prone to infections which may result from injury to surrounding skin by the OTC corn and callus remover drug preparations or by mechanical attempts to remove the corn or callus. Acute inflammation and ulceration may also occur from overuse of OTC corn and callus remover drug products (Refs. *7* and *8*). The Panel also points out that these products should not be used on irritated skin or any area that is infected or reddened.

The Panel adopted the following definitions pertaining to corn and callus removers:

a. *Balm.* A soothing liquid or semisolid preparation.

b. *Collodion.* A solution of pyroxylin (nitrocellulose) in an appropriate nonaqueous solvent which, on application to the skin in a thin layer, leaves a transparent, cohesive film.

c. *Cream base.* A water-in-oil and oil-in-water preparation resulting in a semisolid vehicle.

d. *Emollient.* A bland, fatty, or oily substance which may be applied locally, particularly to the skin, to mucous membranes, or to abraded areas. The skin is rendered softer and more pliable.

e. *Foot salve.* An ointment intended for use on the feet.

f. *Keratolytic agent.* A peeling agent causing a loosening of the cells of the horny layer of the skin.

g. *Lubricant.* Any substance that decreases friction.

h. *Medicated disk.* A topical medication, usually incorporated in a skin-contact adhesive base, carried on a fabric, plastic, or other suitable backing cut to the size and shape appropriate to the lesion to be treated.

i. *Medicated pad.* A topical medication consisting of an appropriately-sized protective pad of fabric, plastic, or other suitable cushioning material in or on which the medication is carried.

j. *Medicated plaster.* A topical medication, usually incorporated in a skin-contact adhesive base, spread upon a fabric, plastic, or other suitable backing.

k. *Ointment base.* A single phase semisolid preparation for external application, which is readily applied to the skin and used primarily as a vehicle or base for the topical application of more active medicinal substances. It may also function as a protectant or emollient.

l. *Vehicle.* A substance utilizated as a carrier for active ingredients. For corn and callus remover active ingredients, it may be an ointment base, solvent, collodion, medicated pad, disk, or plaster.

References

(*1*) Popovich, N. G., "Foot Care Products," *in* "Handbook of Nonprescription Drugs," 5th Ed., American Pharmaceutical Association, Washington, pp. 361–365, 1977.

(*2*) Domonkos, A. N., "Andrews' Diseases of the Skin," 6th Ed., W. B. Saunders Co., Philadelphia, pp. 54–60, 1971.

(*3*) Potter, G. K., "Histopathology of Clavi," *Journal of the American Podiatry Association,* 63:57–66, 1973.

(*4*) Gibbs, R. C., "Skin Diseases of the Feet," Warren H. Green, Inc., St. Louis, pp. 44–62, 1974.

(*5*) Arndt, K. A., "Manual of Dermatologic Therapeutics with Essentials of Diagnosis," 2d Ed., Little, Brown, and Co., Boston, pp. 46–49, 1978.

(*6*) "Stedman's Medical Dictionary," 23d Ed., The Williams and Wilkins Co., Baltimore, 1976, s.v. "corn."

(*7*) Rasmussen, J. E., and A. A. Fisher, "Allergic Contact Dermatitis to a Salicylic Acid Plaster," *Contact Dermatitis,* 2:237–238, 1976.

(*8*) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, p. 909, 1977.

III. Categorization of Data

A. Category I Conditions

These are conditions under which active ingredients used for corn and callus removal are generally recognized as safe and effective and are not misbranded.

1. *Category I ingredient—Salicylic acid.* The Panel concludes that salicylic acid is safe and effective for OTC use as a corn and callus remover when used within the dosage limits stated below.

Salicylic acid, also known as 2-hydroxybenzoic acid and *o*-hydroxybenzoic acid, is found in nature in wintergreen leaves and in the bark of the sweet birch. It is synthesized by heating sodium phenolate with carbon dioxide under pressure. Salicylic acid is

a lipid-soluble drug; 1 gram (g) dissolves in approximately 460 milliliters (mL) water or 15 mL boiling water, 2.7 mL alcohol, 3 mL acetone, 42 mL chloroform, 3 mL ether, 135 mL benzene, 52 mL turpentine, 60 mL glycerin, or 80 mL of fats or oils which makes salicylic acid compatible with a variety of pharmaceutical vehicles (Ref. *1*).

a. *Safety.* Salicylic acid and its derivatives are a widely used group of compounds. They are used as analygesics (pain relievers), antipyretics (fever reducers), keratolytics (peeling agents), rubefacients (agents that cause reddening of the skin), and anti-inflammtory agents. Whether the salicylates are administered orally, rectally, intravenously, or cutaneously, systemic absorption occurs. When salicylates are administered in a toxic dose, the potential side effects are nausea, decreased ability to hear, tinnitus (ringing in the ears), confusion, metabolic disturbances, hallucinations, and, in some extreme cases, death. These toxic reactions are collectively known as salicylism. However, the Panel is unaware of any report of salicylism resulting from the topical use of salicylic acid as a corn and callus remover.

Salicylic acid, when used topically in concentrations of 1 percent and higher, depending on the vehicle, is keratolytic on normal skin and should be applied carefully to hyperkeratotic areas of skin to avoid damage to adjacent healthy skin. It softens and destroys the outer layer of skin by increasing endogenous hydration (water concentration) in this area. This action probably results from lowering the pH and causes the cornified epithelium (horny skin) to swell, soften, and then shed. Necrosis (cell death) of the normal skin has been associated with overuse of salicylic acid (Ref. *2*).

A primary dermal irritation study (Ref. *3*) using a 14-percent concentration of salicylic acid in both acetone collodion and collodion vehicles was performed using the standard Draize Irritation Test on six albino New Zealand rabbits. The procedure for using both test solutions was the same. Application of 0.5 mL of the test material was made to clipped areas of intact and abraded skin. Following application of the test material, the entire trunk of each animal was covered with an impermeable occlusive wrapping. The wrapping and test material were removed and discarded at the end of 24 hours. The skin was examined at 24 and 72 hours following application.

On a scale of 0 to 5, the results of the study showed that 14 percent salicylic acid in acetone collodion gave a primary irritation index of 0.25 (potential for slight irritation, rarely irritating to people, no warning required). Fourteen-percent salicylic acid in collodion gave a primary irritation index of 1.0 (potential for mild irritation, possibly irritating to some people under occlusive wrap conditions, usually no warning required).

A midwestern research department in podiatric medicine conducted two investigations to determine the safety of OTC corn removers containing salicylic acid (Ref. *4*). The first retrospective investigation in September 1976 used completed outpatient medical records for the same year 1974 as a data base. The second investigation, conducted for one week in September 1977, was aimed at the collection of specific and current information on this subject through in-depth interviews. A specifically designed questionnaire was employed as the instrument of the survey and was conducted by a team of doctors on a cross section of the population of Chicago.

The results of the first investigation showed that, of the 3,165 patients who visited the foot clinic in 1974, 2,140 (67.6 percent) were identified as having corns and calluses. A team of researchers carefully examined the clinical histories of each record. A specific search was made for instances where the use of corn removers containing salicylic acid could have been the cause of the clinic visit in 1974. No cases were recorded.

The results of the patient interview survey showed that, out of a total of 953 patients who visited the clinic during the week of the survey, 604 (63.4 percent) had been diagnosed as having corns and calluses. Seventy-two (12 percent) of those 604 patients gave histories of self-medication through the application of corn removers containing salicylic acid. None of the users of such products complained of ever having an adverse reaction which became so severe, in the judgment of the patient, as to necessitate treatment by a doctor. The researchers concluded that there was a complete absence of serious side effects in the cases studied as a result of self-treatment with corn removers containing salicylic acid. This conclusion, in addition to the history of repeated use of such products by many of the patients seen, indicated to the researchers that the application of corn removers containing salicylic acid was safe.

b. *Effectiveness.* Salicylic acid is commonly used by the consumer in OTC preparations for its peeling action in the treatment of hyperkeratotic conditions such as corns and calluses. It is usually formulated in flexible collodion, plasters, disks, or pads.

Flexible collodion contains pyroxylin, in a mixture of ether and alcohol, and plasticizers (camphor and castor oil). Pyroxylin is a nitrocellulose derivative which, after evaporation of the volatile solvents, remains on the skin as an insoluble water-repellant film that adhers better than an aqueous system (Ref. *5*). Flexible collodion is highly flammable and therefore must be stored at room temperature away from heat and must be kept away from fire or flame. Care must also be taken to keep the bottle tightly capped to avoid rapid evaporation of the product and inhalation of the volatile solvents which may cause hypnotic or other undesirable effects.

Collodion, plaster, disk, and pad dosage forms are advantageous because they are adherent and assure contact of the medication with the affected area (Ref. *6*). They also prevent moisture evaporation from the skin, and thereby facilitate penetration of the active ingredient into the affected area resulting in sustained local action of the drug.

Moisture is essential for salicylic acid to exert its action and for maceration and desquamation of epidermal tissue to take place. For that reason, soaking the feet for 15 to 30 minutes and drying before applying the medication aids the keratolytic action of salicylic acid.

A double-blind study was conducted to determine the safety and effectiveness of medicated disks containing 40 percent salicylic acid for the removal of corns and calluses (Ref. *7*). Of the 73 male and female subjects recruited for the study, 54 met the baseline requirements, and 51 completed the study. Subjects were selected for the study if they had at least two lesions, either corns or calluses.

The lesions were classified, graded clinically, measured in size, and rated for pain sensation. Lesions were grouped into paris. Treatments of active drug and placebo were randomly assigned and applied in a double blind fashion. Of the 52 corns and 68 calluses studied, 26 corns and 34 calluses were treated with medicated disks, and the remaining one-half were treated with placebo disks. A total of five applications including the initial application were made in 11 days (at 48- and 72-hour intervals). During each visit the disk was removed, the lesions evaluated, and another disk applied.

The results of the study showed that 19 of the 26 (73 percent) corns treated with the active drug were completely removed as opposed to 1 of 26 (4 percent) treated with the placebo, which was a significant difference. In

considering calluses, 5 of the 34 (15 percent) treated with the active ingredient showed complete removal of the calluses after 11 days as opposed to none in the placebo group. This test statistically demonstrated the effectiveness of the active treatment.

It was impossible to perform this test under truly double-blind conditions because the active formulation produced a characteristic white maceration on normal skin, while the placebo treatment produced only whitening without maceration. This difference could be observed by both the evaluator and the subject.

The study showed that when complete removal of the corn or callus occurred, the freshly exposed areas were red but only slightly tender to touch, and that this redness was not an indication of irritation, but was due to the normal vascular characteristics of freshly exposed skin. It was concluded that the active ingredient was as safe for use on corns and calluses as was the placebo.

The Panel agrees that complete removal of corns and calluses is not always essential because partial removal may provide needed comfort. Therefore, the Panel considers it safer to restrict the application of OTC disks, pads, or plasters to five treatments over a period of not more than 14 days rather than to prolong self-treatment.

A 2-week study with 100 subjects was performed to evaluate the effectiveness of salicylic acid 13.60 percent combined with zinc chloride 2.18 percent in a collodion and castor oil vehicle for the treatment of corns (Refs. *8* and *9*). At the beginning of the study and at all subsequent interviews, the subjects were examined by one consulting dermatologist. The examination consisted of the classification of the location, number, size, and severity, as well as the degree of pain of each subject's corns.

The subjects were randomly divided into 2 equal groups of 50 each. Group I was instructed to apply test medication "X" and test medication "Y" to their corns. Group II was instructed to apply test medication "A" and test medication "B" to their corns. The test medications were coded as follows: "A"—salicylic acid 13.60 percent and 2.18 percent zinc chloride in collodion; "B"—salicylic acid 13.60 percent in a cream base; "X"—proprietary corn and callus remover, salicylic acid concentration unknown; "Y"—salicylic acid 64.5 percent in petrolatum.

The subjects in Group I used test medication "X" on 56 corns and test medication "Y" on 54 corns. The subjects in Group II used test medication "A" on 53 corns and test medication "B" on 53 corns.

The applicants applied the test medications twice daily, once in the morning and once in the evening for 4 days. At the end of the fourth day they were to soak the feet in warm water for 30 minutes, dry the feet, and reapply the test medication. The subjects were told to return to the research laboratory to be reexamined by the consulting dermatologist after using the medication for 7 consecutive days.

At the end of the first week of the study, neither group had obtained 100 percent relief (complete removal of the corn). At the end of the second week of the study, the results showed that 16 percent of the subjects using test medication "X" obtained complete relief, 7.4 percent using test medication "Y" obtained complete relief, 47 percent using test medication "A" obtained complete relief, and 1.9 percent using test medication "B" obtained complete relief.

Based on the current literature, submitted data which includes the results of well-controlled clinical studies, and its own clinical expertise and experience, the Panel concludes that salicylic acid is safe and effective as a keratolytic agent for the treatment of hard corns and calluses at concentrations of 12 to 40 percent in pads, plasters, and disks, and at concentrations of 12 to 17.6 percent in a collodion vehicle. The Panel further concludes that if the hard corn or callus shows no improvement after 2 weeks of treatment, the patient should see a doctor.

For products containing salicylic acid in a collodion vehicle, directions must ensure that the salicylic acid be kept away from the surrounding skin preferably by encircling the corn or callus with a ring of petrolatum. The vehicle used and the accompanying directions must ensure that the salicylic acid is applied only to the corn or callus and is not applied to surrounding normal skin. The Panel cannot recommend the use of salicylic acid in an ointment vehicle for OTC use on corns and calluses because of a lack of data on both safety and effectiveness and classifies salicylic acid formulated in an ointment vehicle as Category II.

The Panel cannot recommend a concentration of salicylic acid which would be safe and effective for removal of soft corns because of insufficient data on both safety and effectiveness and recommends that studies for the treatment of soft corns be undertaken.

c. *Dosage.* Topical dosage is 12 to 40 percent salicylic acid in pads, plasters, and disks, or 12 to 17.6 percent in a collodion vehicle.

d. *Labeling.* The Panel recommends Category I labeling for corn and callus remover active ingredients. (See part III. paragraph A.2. below—Category I labeling.)

References

(*1*) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, p. 1080, 1976.

(*2*) Strakosch, E. A., "Studies on Ointments, II. Ointments Containing Salicylic Acid," *Archives of Dermatology and Syphilology*, 47:16–26, 1943.

(*3*) OTC Volume 160263.

(*4*) OTC Volume 16256.

(*5*) Dittert, L. W., editor, "Sprowls' American Pharmacy," 7th Ed., J. B. Lippincott Co., Philadelphia, p. 167, 1974.

(*6*) Ansel, H. C., "Introduction to Pharmaceutical Dosage Forms," 2d Ed., Lea and Febiger, Philadelphia, pp. 328–329, 1976.

(*7*) OTC Volume 160293.

(*8*) OTC Volume 160003.

(*9*) OTC Volume 160133.

2. *Category I labeling.* The Panel recommends the following labeling for Category I corn and callus remover active ingredients:

a. *Indications.* "For the removal of hard corns and calluses."

b. *Directions*—(1) *For active ingredients formulated in a collodion vehicle.* "Cleanse feet thoroughly with soap. Soak in warm water for 15 to 30 minutes and dry feet thoroughly. Circle corn or callus with a ring of petrolatum to protect surrounding skin. Apply product one drop at a time to sufficiently cover each hard corn or callus only; let dry. Repeat this procedure daily until the corn or callus is removed or partially removed to provide comfort. Do not use medication for more than 14 days."

(2) *For active ingredients formulated in a pad, plaster, or disk dosage form.* "Cleanse feet thoroughly with soap. Soak in warm water for 15 to 30 minutes and dry feet thoroughly. Cut pad, plaster, or disk exactly to cover the corn or callus. Apply the pad, plaster, or disk. Remove pad, plaster, or disk after 48 hours and soak feet for 15 to 30 minutes. If the corn or callus is not soft enough to be removed, repeat the procedure. Do not exceed five treatments over a 14-day period."

c. *Warnings.* (1) "Do not use this product if you are a diabetic or have poor blood circulation because serious complications may result."

(2) "Do not use on irritated skin or on any area that is infected or reddened."

(3) "If discomfort persists, see your doctor."

(4) "Care should be used to avoid contact of product with skin surrounding corn and callus."

(5) "Do not use this product on soft corns."

(6) *For any products containing collodion.* (i) "Highly flammable, keep away from fire or flame."

(ii) "Store at room temperature away from heat."

(iii) "Keep bottle tightly capped."

(iv) "Avoid inhaling vapors."

(v) "If product gets into the eye, flush with water to remove film and continue to flush with water 15 more minutes."

B. Category II Conditions

These are conditions under which active ingredients used for corn and callus removal are not generally recognized as safe and effective or are misbranded.

1. *Category II ingredients.* These ingredients are discussed elsewhere. (See part I. paragraph C.3. above—Other ingredients.)

2. *Category II labeling.* The Panel has examined the submitted labeling claims for corn and callus remover drug products and has classified the following claims as Category II because they are not supported by scientific data:

a. "You are about to make your feet more confortable."

b. "You have just purchased one of the finest foot aids available."

c. "This special liquid preparation helps remove corns quickly."

d. "Walk easy, walk soft."

e. "Other uses for * * * corn pads, chafing, tender spots on sole of foot, instep ridges."

f. "Make walking more pleasurable for you."

g. "Sure to stay in place."

h. "Dissolves corn or callus away."

i. "Lifts off corns." or "Loosens corns."

j. "Absolutely painless."

C. Category III Conditions.

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

1. *Category III ingredients.*

Phenoxyacetic acid
Zinc chloride

a. *Phenoxyacetic acid.* The Panel concludes that phenoxyacetic acid is safe, but there are insufficient data available to determine its effectiveness as an OTC corn and callus remover active ingredient when used within the dosage limits stated below.

Phenoxyacetic acid is also known as phenoxyethanoic acid. It is prepared from phenol and monochloroacetic acid. It has a molecular weight of 152.4. One g is soluble in about 75 mL water; it is freely soluble in alcohol, ether, and benzene (Ref. *1*). Phenoxyacetic acid is not as strong an acid as salicylic acid (K value of 1.06×10^{-3} at 25° C) (Ref. *2*).

(1) *Safety.* A two-phase study was conducted to compare the local toxic effects of phenoxyacetic acid and salicylic acid (Ref. *3*). The experiment was conducted for 30 days on the skin of rabbits to determine the long-term effects and for 3 days on the skin of rats to determine the short-term effects.

Tests ointments of phenoxyacetic acid and salicylic acid were prepared in concentrations of 0.1, 0.3, 1, 5, 10, and 20 percent, and each concentration was applied to the shaved, clipped abdomen and ear of four rabbits. The abdomen was covered by an occlusive bandage. The treated ear was left uncovered. At 2-day intervals the test sites were examined and test preparations reapplied. This procedure was followed for 30 days. At the end of 30 days final inspection of the treated areas was made, the animals were sacrificed, and the tissues were examined histologically.

The results of the first phase of this study showed that both phenoxyacetic acid and salicylic acid, when applied to sensitive rabbit skin in high concentrations (up to 20 percent) for long periods of time (30 days), act as primary irritants. On the basis of both gross and histological evidence, the two preparations appeared to be similar in their irritating effects.

The second phase of the study compared both the relative activity and irritating effects of phenoxyacetic acid with salicylic acid on the skin of adult rats.

Test ointments of phenoxyacetic acid and salicylic acid were prepared in concentrations of 5, 10, 20, and 40 percent. Each concentration was applied to the backs of three white rats after the hair had been closely cut, and the site was then covered with an occlusive wrap. Once a day the skin was inspected. One animal from each concentration group was sacrificed daily, and portions of treated skin were examined for signs of gross irritation.

The results of phase two of the study showed that in concentrations of 5 percent, the onset of the keratolytic effect was seen in 3 days with phenoxyacetic acid. With concentrations of 10 to 40 percent, the onset of activity of phenoxyacetic acid was reduced to 2 days.

With salicylic acid in concentrations of 10 percent, the onset of the keratolytic effect was seen in 3 days. With concentrations of 20 to 40 percent, the onset of activity of salicylic acid was reduced to 2 days.

Concentrations above 20 percent of both salicylic acid and phenoxyacetic acid did not decrease the time of onset of activity or increase signs of irritation.

On the basis of the similar effects of the phenoxyacetic acid and salicylic acid in both phases of the test, the researchers concluded that phenoxyacetic acid could be expected to be no more irritating to hyperkeratotic human skin than salicylic acid in similar concentrations. Salicylic acid has been determined by the Panel to be safe for such use. (See part III. Paragraph A.1. above—Category I ingredient—Salicylic acid.)

In a study performed on both men and women with corns and calluses, test preparations were applied using 40 percent phenoxyacetic acid in 30 percent silicone fluid and 40 percent salicylic acid in 30 percent silicone fluid (Ref. *3*). Sixty-two corns and 62 calluses were treated with phenoxyacetic acid, and 36 corns and 47 calluses were treated with salicylic acid.

The medications were incorporated into identical standard corn and callus pads. At the beginning of the experiment the feet of each patient were carefully examined and detailed records prepared. Experimental pads were then placed on the lesions and were left on for 72 hours. At the end of this period, the pads were removed at the clinic, and the sites examined.

Throughout the clinical study no case of primary irritation due to phenoxyacetic acid was noted. Evidence of irritation was noted in three patients with salicylic acid

The conclusions drawn by the researcher was that phenoxyacetic acid was safe for consumer use as an OTC corn and callus active ingredient because of the lack of occurrence of primary irritation.

(2) *Effectiveness.* Two studies were conducted in 1948 to compare the effectiveness of 40 percent salicylic acid to the effectiveness of 40 percent phenoxyacetic acid contained in one type of corn pad (Ref. *3*). In the first study 62 corns and 62 calluses were treated with phenoxyacetic acid, and 36 corns and 47 calluses were treated with salicylic acid.

The results of the study showed that phenoxyacetic acid was 95.1 percent effective in the treatment of corns, while salicylic acid was 72.2 percent effective. Phenoxyacetic acid was 77.4 percent effective, and salicylic acid was 74.5 percent effective in the treatment of calluses.

In the second study, 33 corns were treated with a plaster containing 40 percent phenoxyacetic acid, and 33 additional corns were treated with a plaster containing 40 percent salicylic acid. The plasters were allowed to remain on the corns for 72 hours. If a second application was necessary, a second plaster was applied and allowed to remain for 72 hours. The final results were satisfactory (either complete or partial removal) to 76 percent of the subjects using plasters with phenoxyacetic acid and to 79 percent of subjects using plasters with salicylic acid. However, the method used in evaluating the "activity" of phenoxyacetic acid and salicylic acid in these tests is open to question. The method of scoring depended on the extent to which the corn could be removed by the patient after 72 hours of treatment. The effectiveness of the product, therefore, depended first upon the dexterity and the vigor used by the patient in removing the corn, and second upon the ability of the observer to decide when the core of the corn had been removed.

The Panel concludes that there are insufficient data to establish that phenoxyacetic acid is effective as an OTC corn and callus remover active ingredient.

(3) *Proposed dosage.* Topical dosage is 40 percent phenoxyacetic acid in pads, plasters, or disks.

(4) *Labeling.* The Panel recommends Category I labeling. (See part III. paragraph A.2. above—Category I labeling.)

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, p. 943, 1976.

(2) Heilbron, I., and H. M. Bunbury, "Dictionary of Organic Compounds," Volume 4, Oxford University Press, New York, p. 2663, 1965.

(3) OTC Volume 160294.

b. *Zinc chloride.* The Panel concludes that zinc chloride is safe, but there are insufficient data available to determine its effectiveness as an OTC corn and callus remover active ingredient when used within the dosage limits stated below.

Zinc chloride occurs as a white or nearly white, odorless substance taking various forms such as a crystalline powder, porcelain-like masses, or fused sticks or pencils. It has a molecular weight of 136.29, and a density of about 2.907. It melts at about 290° C and boils at 732° C. One g dissolves in 0.5 mL water, in about 1.5 mL alcohol at 25° C, in 0.25 mL of 2 percent hydrochloric acid, in 2 mL glycerin, and is fairly soluble in acetone and soluble in ether. An aqueous solution of 10 percent zinc chloride has a pH of about 4 and is acid to litmus (Refs. *1* and *2*).

Zinc chloride is chemically produced by reacting metallic zinc or zinc oxide with hydrochloric acid and evaporating the solution to a dry state (Refs. *1, 2,* and *3*).

(1) *Safety.* Zinc chloride has been safely used as a caustic, astringent, antibacterial, antiperspirant, and a tooth desensitizer (Refs. *1, 4, 5,* and *6*).

One study was performed to determine the primary irritation index of 2.2 percent zinc chloride in collodion (Ref. *5*). The test was conducted on six albino New Zealand rabbits, three male and three female. The test method was essentially that of the standard Draize Irritation Test. Applications of 0.5 mL of the test material were made on clipped areas of intact and abraded skin. The abrasions were only deep enough to penetrate the outer layer.

Following application of the test material, the entire trunk of each animal was covered with an impermeable occlusive wrapping. The wrappings were removed 24 hours after the application of the test material. The test sites were individually examined and scored separately at 24 and 72 hours. The results gave a primary irritation index of 1.60 (a potential for mild irritation which may be possibly irritating to some people under occlusive wrap conditions).

Based on the current literature and its own clinical expertise and experience, the Panel concludes that zinc chloride is safe as an OTC corn and callus remover active ingredient.

(2) *Effectiveness.* Zinc chloride applied as a paste in a concentration of 30 to 40 percent destroys tissues. Mohs (Ref. *7*) reported that zinc chloride was used to destroy external malignant lesions. Layers of dead tissue were excised after each application until normal tissue was reached.

In low concentrations (2.2 percent) zinc chloride, like most of the other metallic salts, is not strong enough for use as a caustic (Ref. *4*).

The Panel is not aware of any data available on zinc chloride as a single active ingredient for use as an OTC corn or callus remover, but it is a component of a reviewed combination. (See part III. paragraph D. 3. below—Category III combination.)

The Panel concludes there are insufficient data to establish the effectiveness of zinc chloride as an OTC corn and callus remover active ingredient.

(3) *Proposed dosage.* Topical dosage is 2.2 percent zinc chloride in collodion.

(4) *Labeling.* The Panel recommends Category I labeling. (See part III. paragraph A.2. above—Category I labeling.)

References

(1) Harvey, S. C., "Topical Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., Edited by A. Osol et al., Mac Publishing Co., Easton, PA, p. 719, 1975.

(2) Wade, A., and J. E. F. Reynolds, editors, "Martindale. The Extra Pharmacopoeia," 27th Ed., The Pharmaceutical Press, London, p. 221, 1977.

(3) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, p. 1307, 1976.

(4) Soine, T. O., and C. O. Wilson, "Rogers' Inorganic Pharmaceutical Chemistry," 8th Ed., Lea and Febiger, Philadelphia, pp. 410–413, 1967.

(5) OTC Volume 160283.

(6) Sonneland, J., "The 'inoperable' Breast Carcinoma, A Successful Result using Zinc Chloride Fixative," *The American Journal of Surgery,* 124:391–393, 1972.

(7) Mohs, F. E., "Chemosurgical Treatment of Melanoma; Microscopically Controlled Method of Excision," *Archives of Dermatology and Syphilology,* 62:269–279, 1950.

2. *Category III labeling.* None.

D. Combination Policy

The Panel has reviewed and concurs with the rationale expressed in the combination drug policy for OTC products as set forth in 21 CFR 330.10(a)(4)(iv):

> 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.

The Panel classified the combinations of active ingredients submitted to it as follows:

1. *Category I combinations.* None.

2. *Category II combinations—Salicylic acid and local anesthetics.* The Panel concludes that salicylic acid is safe and effective. (See part III. paragraph A.1. above—Category I ingredient—Salicylic acid.) However, the Panel concludes that pain from keratolytic action of salicylic acid on subcutaneous tissue and developing infections may be masked by local anesthetic used in combination with salicylic acid so that the consumer would not be alerted to potential danger. Such combinations are therefore considered unsafe.

3. *Category III combination—Salicylic acid and zinc chloride.* The Panel concludes that salicylic acid is safe and effective. (See Part III. paragraph A.1. above—Category I ingredient—Salicylic acid.) However, there is no evidence to establish that zinc chloride contributes to the effectiveness of the combination of salicylic acid and zinc chloride as a corn and callus remover. This combination has been discussed elsewhere. (See part III. paragraph C.1.b. above—Zinc chloride.) The Panel is also concerned about the possible formation of zinc salicylate in this combination. The Panel recommends that chemical stability tests be conducted as part of any Category III testing. Salicylic acid is not effective when incorporated in a zinc oxide paste because of the formation of zinc salicylate which is pharmacologically inactive (Ref. *1*).

Reference

(*1*) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, p. 909, 1977.

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 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 (see 46 FR 26052; May 11, 1981), the agency advises in this advance notice of proposed rulemaking that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations would be amended by adding in Part 358, new Subpart F, to read as follows:

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

Subpart F—Corn and Callus Remover 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 F—Corn and Callus Remover Drug Products

§ 358.501 Scope.

(a) An over-the-counter corn and callus remover drug product in 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.

§ 358.503 Definitions.

As used in this subpart:

(a) *Corn and callus remover drug product.* A topical agent used for the removal of hard corns and calluses.

(b) *Collodion.* A solution of pyroxylin (nitrocellulose) in an appropriate nonaqueous solvent which, on application to the skin in a thin layer, leaves a transparent, cohesive film.

(c) *Medicated disk.* A topical medication, usually incorporated in a skin-contact adhesive base, carried on a fabric, plastic, or other suitable backing cut to the size and shape appropriate to the lesion to be treated.

(d) *Medicated pad.* A topical medication consisting of an appropriately sized protective pad of fabric, plastic, or other suitable cushioning material in or on which the medication is carried.

(e) *Medicated plaster.* A topical medication, usually incorporated in a skin-contact adhesive base, spread upon a fabric, plastic, or other suitable backing.

§ 358.510 Corn and callus remover active ingredients.

(a) Salicylic acid 12 to 40 percent in pads, plasters, and disks.

(b) Salicylic acid 12 to 17.6 percent in collodion.

§ 358.550 Labeling of corn and callus remover drug products.

(a) *Statement of identify.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "corn and callus remover."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "indications" that is limited to the following phrase: "For the removal of hard corns and calluses."

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

(1) *For products containing any ingredient identified in § 358.510.* (i) "Do not use this product if you are a diabetic or have poor blood circulation because serious complications may result."

(ii) "Do not use on irritated skin or on any area that is infected or reddened."

(iii) "If discomfort persists, see your doctor."

(iv) "Care should be used to avoid contact of product with skin surrounding corn and callus."

(v) "Do not use this product on soft corns."

(2) *For any products containing collodion.* (i) "Highly flammable, keep away from fire or flame."

(ii) "Store at toom temperature away from heat."

(iii) "Keep bottle tightly capped."

(iv) "Avoid inhaling vapors."

(v) "If product gets into the eye, flush with water to remove film and continue to flush with water 15 more minutes."

(d) *Directions*—(1) *For products containing salicylic acid identified in § 358.510(a).* "Cleanse feet thoroughly with soap. Soak in warm water for 15 to 30 minutes and dry feet thoroughly. Cut pad, plaster, or disk exactly to cover the corn or callus. Apply the pad, plaster, or disk. Remove pad, plaster, or disk after 48 hours and soak feet for 15 to 30 minutes. If corn or callus is not soft enough to be removed, repeat the procedure. Do not exceed five treatments over a 14-day period."

(2) *For products containing salicylic acid identified in § 358.510(b).* "Cleanse feet thoroughly with soap. Soak in warm water for 15 to 30 minutes and dry feet thoroughly. Circle corn or callus with a ring of petrolatum to protect surrounding skin. Apply product one drop at a time to sufficiently cover each hard corn or callus only; let dry. Repeat this procedure daily until corn or callus is removed or partially removed to provide comfort. Do not use medication for more than 14 days."

Interested persons may, on or before April 5, 1982, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before May 5, 1982. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: September 23, 1981.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Dated: December 17, 1981.

Richard S. Schweiker,

Secretary of Health and Human Services.

[FR Doc. 82–4 Filed 1–4–82; 8:45 am]

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