DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 358

[Docket No. 81N-0122]

Corn and Callus Remover Drug Products for Over-the-Counter Human Use; Tentative Final Monograph

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

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

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by April 21, 1987. New data by February 20, 1988. Comments on the new data by April 20, 1988. These dates are consistent with the time periods specified in the agency's revised procedural regulations for reviewing and classifying OTC drugs (21 CFR 330.10). Written comments on the agency's economic impact determination by June 22, 1987.

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

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drugs and Biologics (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION: In the Federal Register of January 5, 1982 (47 FR 522), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC corn and callus remover drug products, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by April 5, 1982. Reply comments in response to comments filed in the initial comment period could be submitted by May 5, 1982.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information.

In response to the advance notice of proposed rulemaking, one manufacturer submitted comments. Copies of the comments received are on public display in the Dockets Management Branch.

In order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10), the present document is designated as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule) to establish Subpart F of Part 358 (21 CFR Part 358, Subpart F), FDA states for the first time its position on the establishment of a monograph for OTC corn and callus remover drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC corn and callus remover drug products.

This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC corn and callus remover drug products as modified on the basis of the comment received and the agency's independent evaluation of the Panel's report. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them.

The OTC procedural regulations (21 CFR 330.10) now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA will no longer use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but will use instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

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

In the advance notice of proposed rulemaking for OTC corn and callus remover drug products (published in the **Federal Register** of January 5, 1982; 47 FR 522), the agency suggested that the conditions included in the monograph (Category I) be effective 6 months after the date of publication of the final monograph in the **Federal Register**. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 6 months after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products will have to be reformulated to comply with the

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

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss, but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the **Federal Register**. The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and reformulate their products and have them in compliance in the marketplace.

If the agency determines that any labeling for a condition included in the final monograph should be implemented sooner than the 12-month effective date, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

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

I. The Agency's Tentative Conclusions on the Comments

A. Comments on Ingredients

1. In response to the Panel's statement at 47 FR 527 that it could not 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, one comment submitted several studies to support the safety and effectiveness of salicylic acid for the removal of soft corns (Refs. 1, 2, and 3). The comment stated that the results of these clinical studies convincingly demonstrate that salicylic acid provides clinically and statistically significant improvement in the removal of soft corns. The comment requested that salicylic acid for the removal of soft corns be included in the monograph.

The agency has evaluated these studies and concludes that they are sufficient to support the safe and effective use of salicylic acid for the removal of soft corns. In a double-blind, placebo-controlled dose range study, adhesive disks impregnated with salicylic acid at concentrations of 12, 20, 30, and 40 percent were compared with a placebo (Ref. 2). Over a 10-day study period with a 2-day post treatment evaluation, four applications of the appropriate concentrations were made to subjects at 48-hour intervals (72 hours, if an application occurred on a Friday). One soft corn per subject was treated. Results of the study indicated that all four concentrations of salicylic acid were statistically superior to the placebo in removing the soft corns, but not statistically significantly different from each other in efficacy. All active treatment groups required 8 days of treatment (three applications) to obtain maximum response. No clinically significant adverse reactions were reported during the study. The safety of treatments was measured by the incidence of erythema before and after attempted removal of the corn. Analysis of the data indicated that the different concentrations of salicylic acid and placebo had no direct effect on erythema. The erythema reported in the study was primarily a function of physical response to the corn removal and was not accompanied by discomfort.

In another double-blind, placebo-controlled study (Ref. 1), 12 percent salicylic acid impregnated in a disk plaster was evaluated for the removal of soft corns and subsequent relief of pain. Sixteen subjects provided 20 cases of soft corns. Ten cases were treated with 12 percent salicylic acid and 10 cases were treated with placebo. A maximum of three 48-hour applications was made to each subject. Statistical analysis of the salicylic acid data showed a significant difference between pretest and post test values for the parameters studied, i.e., lesion size, hyperkeratosis, and pain. No significant difference between pretest and post test values for the parameters analyzed was shown for placebo. No adverse reactions were noted in any of the subjects during the study.

A third double-blind, placebo-controlled study (Ref. 3) was designed to evaluate the safety and efficacy of adhesive disks impregnated with 20 percent salicylic acid and to evaluate the effect of soaking the corn (after treatment and prior to attempted removal) as a means of increasing efficacy. Treatment consisted of four 48-hour applications over a 10-day period with a 2-day post-treatment evaluation. Sixty-three subjects using either drug or placebo were divided into three groups with Group I soaking the corn for 5 minutes; group II soaking for 15 minutes; and group III soaking for 5 minutes, after which a soft bristle brush was used in an attempt to loosen the corn. The groups soaked the corns after each 48-hour treatment (72 hours, if an application occurred on a Friday). Efficacy was assessed on the bases of rate of corn removal, clinical grade, and size of corn. Sixty patients, 20 in each of the three groups, completed the study. Results of the study indicated that 19 out of 30 (63.3 percent) using the 20-percent salicylic acid had their corns completely eliminated by the end of the treatment period, regardless of the soaking technique. Of the patients on the placebo, one (3.3 percent) obtained complete removal. No consistently significant soaking effects were found for any efficacy parameter assessed. No clinically significant adverse reactions were reported during the study. The degree of erythema was assessed before and after attempted removal as a measure of irritation or safety of the treatment. Although erythema was greater for the 20-percent salicylic acid group than for the placebo group, it appears that the erythema is a result of the removal of the corn and exposure of underlying tissue rather than due to the reaction to salicylic acid. Based on the results of the studies cited above, the agency concludes that salicylic acid is safe and effective for the removal of soft corns. Thus, the warning recommended by the Panel in § 358.550(c)(1)(v) against use of salicylic acid on soft corns is being deleted.

The agency notes that hard and soft corns differ only in their anatomical location. The etiology, pathology, and physiology for hard corns and soft corns are basically the same (Ref. 4). Thus, the agency can find no rationale for distinguishing between hard and soft corns with respect to drug treatment and labeling based solely on their anatomical location. In addition, based on the new data reviewed by the agency establishing the safety and effectiveness of salicylic acid for the removal of soft corns, the Panel's recommended limitation to "hard" corns in the definition of a corn and callus remover drug product (§ 358.503(a)) and in the labeling indications (§ 358.550(b)) is not being included in this tentative final monograph. Accordingly, the definition of a corn and callus remover drug

product has been revised to read, "A topical agent used for the removal of corns and calluses," and the indication for use for these products has been revised to read, "For the removal of corns and calluses."

Based on the studies discussed above, the agency is proposing that salicylic acid 12 to 40 percent in medicated plaster vehicles and salicylic acid 12 to 17.6 percent in a collodion-like vehicle be generally recognized as safe and effective for the removal of corns and calluses. It should be noted that the agency is proposing to revise the descriptive terms for the vehicles of administration. Because medicated disks, pads, and plasters are similar in nature, the agency does not see a need to have separate definitions in the monograph. Thus, the agency is combining these definitions into a single definition that includes all three dosage forms and is proposing in this tentative final monograph to use the term "plaster" to include "disk" and "pad."

The agency notes that the Panel designated collodion as the vehicle for liquid formulations of salicylic acid. Collodion is an official article in the United States Pharmacopeia (U.S.P.) (Ref. 5). In reviewing the labeling of marketed corn/callus remover drug products, the agency has determined that some formulations (Refs. 6, 7, and 8) contain flexible collodion, which is also an official U.S.P. article, and which contains camphor and castor oil in collodion (Ref. 5). In addition, the agency has determined that some formulations contain other inactive ingredients or varying amounts of solvent (e.g., ether, alcohol, acetone, castor oil) which provide for increased spreadability and increased pliability of the product after it dries on the skin (Refs. 6, 9, 10, and 11). Therefore, the agency is proposing to use the term "collodion-like" instead of "collodion" in specifying the vehicle for liquid formulations and is defining "collodion-like vehicle" as follows: "A solution containing pyroxylin (nitrocellulose) in an appropriate nonaqueous solvent that leaves a transparent cohesive film when applied to the skin in a thin layer."

References

(1) Karas, A. A., "A Pilot Study on the Safety and Effectiveness of a Formulation for the Removal of Soft Corns and Subsequent Relief of Pain," (IBT No. 636-03794), draft of unpublished study, Comment No. C00001, Docket No. 81N-0122, Dockets Management Branch.

(2) Reed, M. L., "Evaluation of Safety and Efficacy of Salicylic Acid for the Removal of Soft Corns," (Scholl Study No. S-82-6), draft of unpublished study, Comment No. LET, Docket No. 81N-0122, Dockets Management Branch.

(3) Goodman, J. J., and L. Farris, "Evaluation of Safety and Efficacy of 20% Salicylic Acid for the Removal of Soft Corns," (Scholl Study No. S-82-47), draft of unpublished study, Comment No. LET, Docket No. 81N-0122, Docket Management Branch.

(4) Popovich, N., "Foot Care Products," *in* "Handbook of Nonprescription Drugs," 7th Ed., American Pharmaceutical Association, Washington, p. 616, 1982.

(5) "United States Pharmacopeia XXI—National Formulary XVI," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 248, 1985.

(6) OTC Volume 160097.

(7) "Handbook of Nonprescription Drugs," 7th Ed., American Pharmaceutical Association, Washington, p. 640, 1982.

(8) "American Drug Index," 30th Ed., J. B. Lippincott Co., Philadelphia, p. 267, 1986.

(9) OTC Volume 160003.

(10) OTC Volume 160133.

(11) OTC Volume 160283.

B. Comments on Labeling

2. One comment suggested the following as examples of other appropriate labeling indications for corn and callus remover drug products: (1) "For treatment of hard corns and calluses," and (2) "For relief of pain associated with hard corns and calluses." With respect to the second suggested indication, the comment stated that it seems appropriate to inform consumers that if the corn is removed, the pain associated with the corn will also be relieved. The comment added that many corn and callus remover drug products are sold with a variety of nonmedicated pads that are used to cushion the area surrounding the corn. The comment contended that these pads, which are actually medical devices, also help to relieve pain by a mechanism unrelated to the actual removal of the corn.

With respect to the first suggested indication, the agency recognizes that the intended result from use of the product is the "removal" of the affected skin rather than the "treatment" or cure of the condition; thus, the word "treatment" does not clearly convey to the consumer the intended action of the product. In comment 1 above, the agency is proposing to remove the Panel's recommended restrictions on using these products only on hard corns. Therefore, the agency believes that the indication "For removal of corns and calluses" is more clear in describing the intended action of corn and callus remover drug products than is the wording proposed by the comment.

With regard to the second suggested indication, "For relief of pain associated with hard corns and calluses," the agency is unaware of any data to demonstrate that, when applied externally, these products act to relieve pain by exerting an analgesic or anesthetic effect. However, the agency acknowledges that pain is a symptom of the condition and may be indirectly relieved when corns and calluses are removed (see comment 1, Ref. 1). Therefore, the agency is proposing that the secondary indication "Relieves pain by removing corns and calluses" be permitted only in conjunction with the primary indication "For removal of corns and calluses" discussed above. Because OTC drug monograph labeling covers only the drug use of the active ingredient in the product, the indication included in the monograph does not apply to the use of nonmedicated pads included with the product because nonmedicated pads are regulated as devices under the Federal Food, Drug, and Cosmetic Act.

3. One comment contended that although the Panel's recommended indication "For the removal of hard corns and calluses"' in § 358.550(b) is an accurate description of the proper use of salicylic acid, there are other equally meaningful ways to state the indications. The comment suggested that the introductory wording in § 358.550(b) be changed from the restrictive statement ". . . limited to the following phrase . . .," to read, "Indications. The labeling of the product contains a statement of the indications under the heading 'indications' *such as*: 'For the removal of hard corns and calluses.' "

In the **Federal Register** of May 1, 1986 (51 FR 16258), the agency published a final rule changing its labeling policy for stating the indications for use of OTC drug products. Under the final rule, the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either (1) the specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "APPROVED USES"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "APPROVED USES"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "APPROVED USES," plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. The proposed rule in this document is subject to the final rule revising the labeling policy. Accordingly, the restrictive statement

". . . limited to the following phrase . . ." is not included in this proposal.

4. One comment contended that the Panel erroneously expanded the scope of Category II by inappropriately including statements describing product performance rather than "conditions" that would result in the drug not being generally recognized as safe and effective or would result in misbranding. The comment contended that such statements as "You are about to make your feet more comfortable," and "Make walking more pleasurable for you," are merely describing desired results of use of the product and are not Category II conditions. The comment also pointed out that several corn/callus products are sold as a combination kit containing a drug (the medicated disks) and a medical device (the unmedicated pads, cushions, etc.). The comment contended that the statement "Other uses for . . . corn pads, chafing, tender spots on sole of foot, instep ridges" is a proper statement for the additional "intended uses" of the medical device and, therefore, is not a Category II condition. Regarding the statement "Sure to stay in place," the comment maintained that this statement relates to the physical attributes of the adhesive used to secure the pads, and is not a condition for which the product should be judged safe or effective.

The OTC drug review program establishes conditions under which OTC drugs are generally recognized as safe and effective and not misbranded. Two principal conditions examined during the review are allowable ingredients and allowable labeling. FDA has determined that it is not practical—in terms of time, resources, and other considerations—to set standards for all labeling found in OTC drug products. Accordingly, OTC drug monographs regulate only labeling related in a significant way to the safe and effective use of covered products by lay persons. OTC drug monographs establish allowable labeling for the following items: product statement of identity; names of active ingredients; indications for use; directions for use; warnings against unsafe use, side effects, and adverse reactions; and claims concerning mechanism of drug action.

The agency agrees that the statements referred to by the comment do not relate in a significant way to the drug's safe and effective use and are outside the scope of the OTC drug review. Such statements will be evaluated by the agency on a product-by-product basis, under the provisions of section 502 of the act (21 U.S.C. 352) relating to labeling that is false or misleading. Moreover, any statement that is outside the scope of the monograph, even though it is truthful and not misleading, may not appear in any portion of the labeling required by the monograph and may not detract from such required information. However, statements and terms outside the scope of the monograph may be included elsewhere in the labeling, provided they are not false or misleading.

5. One comment suggested that the recommended warnings for products containing collodion, in § 358.550(c)(2)(i), "Highly flammable, keep away from fire or flame," and (ii), "Store at room temperature away from heat," could be easily combined. The comment also suggested that, even though 16 CFR 1500.81(a) specifically exempts drugs from hazardous substances labeling, an appropriate "signal word" similar to those in 16 CFR 1500.3(b)(10) (extremely flammable, flammable, or combustible) should be used depending on the actual flashpoint of the product. The comment recommended that the combined warning read as follows: "'signal word,' keep away from fire, or excessive heat."

FDA believes that the warning statements are intended to convey two distinct messages, i.e., (1) the proper use of the product because of its flammable nature and (2) the proper storage conditions because of the volatile nature of the product. For these reasons and because the comment does not provide sufficient reason for combining the warnings, FDA believes that the warning statements on flammability and on storage at room temperature should be stated separately. FDA does agree, however, with the comment that labeling similar to the hazardous substances labeling (16 CFR Part 1500) is appropriate for OTC corn and callus remover drug products formulated in a flammable vehicle.

Even though the regulations in 16 CFR 1500.81(a) provide an exemption for drugs, FDR concurs with the definitions of "signal words," i.e., extremely flammable, flammable, and combustible, based on the flashpoint of the product as defined in 16 CFR 1500.3(b)(10). Therefore, the agency is proposing that the labeling of OTC corn and callus remover drug products formulated in a flammable vehicle contain an appropriate flammability warning consistent with the requirements of 16 CFR Part 1500 and that an appropriate "signal word" based on the flashpoint of the product as defined in 16 CFR 1500.3(b)(10) be used. In addition, the agency is proposing that the warning section of the labeling also include the statement "Keep away from fire or flame."

6. One comment suggested that the warnings recommended by the Panel in § 358.550(c) could be combined to avoid duplicative phrases and to give more prominence to their substance by eliminating excess replication of common phrases. The comment requested that § 358.550(c) be reworded to be similar to the warnings language recommended in the advance notice of proposed rulemaking for OTC internal analgesic, antipyretic, and antirheumatic drug products (42 FR 35493) which states that "the labeling of the product contains the appropriate warnings under the heading 'Warnings' which may be combined to eliminate duplicative words or phrases so the resulting warning is clear and understandable as follows: . . . ."

The agency has reviewed the Panel's recommendations in § 358.550(c) and is proposing to combine, revise, or delete a number of the warnings (see comments 1 above and 7 and 8 below). In addition, the agency is proposing to combine the warnings on storage and capping (§ 358.550(c)(2)(ii) and (iii)) to read "Cap bottle tightly and store at room temperature away from heat." The agency is also proposing to shorten the warning in § 358.550(c)(2)(v) from "If product gets into the eye, flush with water to remove film and continue to flush with water 15 more minutes" to read, "If product gets into the eye, flush with water for 15 minutes." The agency believes that in light of these proposed revisions in the warning section, it is unnecessary to include the statement on allowing warnings to be combined to eliminate duplicative words or phrases, as requested by the comment.

7. One comment suggested that the recommended warning in § 358.550(c)(1)(iii), which advises consumers to consult a doctor if discomfort persists, be modified to read, "If discomfort persists, see your doctor or podiatrist." The comment contended that because corns and calluses are often treated by podiatrists as well as by physicians, it seems reasonable and appropriate to direct the consumer to either if problems occur.

The agency agrees with the comment that it would be appropriate to include "podiatrist" in the warnings for corn and callus remover drug products because a podiatrist is a medical specialist who treats problems of the feet. Therefore, the agency is proposing to revise the labeling in this tentative final monograph to include the term "podiatrist" together with the term "doctor." This approach is similar to

including the term "dentist" in addition to the term "doctor" in the labeling of products intended primarily for dental use.

8. Agreeing in substance that the recommended warning in § 358.550(c)(1)(i), i.e., "Do not use this product if you are a diabetic or have poor blood circulation because serious complications may result," is appropriate, one comment suggested that the words "because serious complications may result," be deleted. The comment contended that the latter part of the warning did not add anything and was unnecessary because it did not specify what complications may result. The comment asserted that any warning, if ignored, would result in serious complications.

The agency agrees with the comment that the phrase "because serious complications may result" is unnecessary. Further, the agency believes that the special health needs of people with diabetes or poor blood circulation can best be evaluated by trained health professionals. Therefore, the agency is proposing to revise the warning in § 358.550(c)(1)(i) to read as follows: "Do not use this product if you are a diabetic or have poor blood circulation except under the advice and supervision of a doctor or podiatrist." (See also comment 7 above.)

9. One comment stated that the Panel's recommended directions in § 358.550(d) (1) and (2) are generally acceptable for these products, but in some respects do not reflect the findings of recent data and are not representative of actual product use. For example, the comment stated that although soaking may enhance the efficacy of salicylic acid in removing corns, study results indicated that the efficacy of salicylic acid is not dependent on soaking. Therefore, there is no need for extended soaking periods before or after treatment. Likewise, recent data show that there is no need when using a collodion-like salicylic acid product to encircle the corn or callus with petrolatum because salicylic acid does not harm normal skin (Refs. 1, 2, and 3). The comment added that the petrolatum ring would add a messy (and perhaps unnecessary) step that would reduce patient compliance and suggested instead that the directions be modified to instruct the consumer to immediately wipe off any excess product which may spread to the tissue surrounding the corn/callus. Additionally, the comment stated that the once-a-day, 14-day treatment regimen for collodion-like products should be changed to twice-a-day treatment for no more than 4 days. The comment referred to a study discussed in the Panel's report at 47 FR 527, as well as the marketing experience of a product, in support of this request.

After review and evaluation of the comment's suggestions, along with the submitted data, the agency agrees that the directions for use should be revised. The directions for use in this tentative final monograph will not include recommendations for soaking. The results of a double-blind placebo-controlled study, in which the effect of soaking as a means of increasing efficacy of salicylic acid was evaluated, demonstrated no clinically or statistically significant differences between the soaking and the nonsoaking groups (Ref. 4). (See also comment 1 above.)

The Panel's recommended directions requiring the corn or callus to be encircled with petrolatum are also not being included in this tentative final monograph. Recent studies on the effect of salicylic acid on normal skin have demonstrated that salicylic acid primarily reduces the intercellular cohesiveness of the horny cells and has no effect on the mitotic activity of the normal epidermis (Refs. 2 and 3). Thus, the Panel's recommended warning in § 358.550(c)(1)(iv) regarding avoiding contact with surrounding skin is not being included in this tentative final monograph. In addition, the vehicles of corn/callus remover drug products are designed to deliver the drug to the affected site. Therefore, the agency believes it is sufficient to instruct consumers to apply the product to the affected site and, based on the data discussed above, does not believe that a statement regarding wiping off excess from tissue surrounding the corn/callus is necessary for collodion-like products, as the comment suggested. Additionally, because corn and callus remover drug products may be used on areas other than the feet, e.g., calluses that occur on the hands, the directions for use are being modified to delete specific reference to the feet.

After a review of submitted data and marketed products, the agency has revised the dosage regimen for salicylic acid in collodion-like drug products from once-a-day for no more than 14 days to once or twice a day as needed for no more than 14 days. Although the comment suggested a much shorter time, no data were submitted to support the request. The agency notes that the study referred to by the comment and cited at 47 FR 527 in support of the twice-a-day, 4-day regimen, was actually a twice-a-day, 14-day study, with efficacy assessed at the end of 14 days, not at 4 days.

Based on the discussion above, the directions proposed in this tentative final monograph are as follows:

(1) *For products containing salicylic acid formulated in a plaster vehicle.* "Wash affected area and dry thoroughly." (If appropriate: "Cut plaster to fit corn/callus.") "Apply medicated plaster. Repeat this procedure every 48 hours as needed (until corn/callus is removed) for up to 14 days."

(2) *For products containing salicylic acid formulated in a collodion-like vehicle.* "Wash affected area and dry thoroughly. Apply one drop at a time to sufficiently cover each corn or callus. Let dry. Repeat this procedure once or twice daily as needed (until corn/callus is removed) for up to 14 days."

References

(1) Davies, M., and R. Marks, "Studies on the Effect of Salicylic Acid on Normal Skin," *British Journal of Dermatology*, 95:187–192, 1976.

(2) Huber, C., and E. Christophers, "'Keratolytic' Effect of Salicylic Acid," *Archives for Dermatological Research*, 257:293–297, 1977.

(3) Roberts, D. L., R. Marshall, and R. Marks, "Detection of the Action of Salicylic on the Normal Stratum Corneum" *British Journal of Dermatology*, 103:191–196, 1980.

(4) Goodman, J. J., and L. Farris, "Evaluation of Safety and Efficacy of 20% Salicylic Acid for the Removal of Soft Corns," (Scholl Study No. S–82–47), draft of unpublished study, Comment No. LET, Docket No. 81N–0122, Dockets Management Branch.

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

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

1. *Summary of ingredient categories.* The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and has made no changes in the categorization of corn and callus remover active ingredients recommended by the Panel. As a convenience to the reader, the following list is included as a summary of the categorization of corn and callus remover active ingredients recommended by the Panel and the proposed categorization by the agency.

Corn and callus remover active ingredients	Panel	Agency
Acetic acid, glacial	II	II
Allantoin (5-ureidohydantoin)	II	II
Ascorbic acid	II	II
Belladonna (extract) (alkaloids of belladonna).	II	II

Corn and callus remover active ingredients	Panel	Agency
Chlorobutanol	II	II
Piperodon hydrochloride	II	II
Ichthammol (ichthyol)	II	II
Iodine	II	II
Methylbenzethonium chloride	II	II
Methyl salicylate	II	II
Panthenol	II	II
Phenoxyacetic acid	III	III
Phenyl salicylate (salol)	II	II
Salicylic acid	I	I
Vitamin A	II	II
Zinc chloride	III	III

2. *Testing of Category II and Category III conditions.* Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any corn and callus remover ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the **Federal Register** of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). That policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

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

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

1. Based on data submitted in support of the safety and effectiveness of salicylic acid for the removal of soft corns, the agency is proposing that products covered by the monograph not be limited to the removal of hard corns and calluses. (See comment 1 above.)

2. Because medicated disks, pads, and plasters are similar in nature, the agency is proposing to use the term "plaster" to include "disk" and "pad." In addition, the agency is proposing to use the term "collodion-like" in place of "collodion" because marketed liquid formulations contain ingredients other than those included in the U.S.P. article. Thus, the agency is proposing a number of revised definitions in this tentative final monograph. (See comment 1 above and § 358.503 below.)

3. The agency is proposing to allow use of the secondary indication "For relief of pain associated with corns and calluses" but only in conjunction with the primary indication "For removal of corns and calluses." (See comment 2 above.)

4. The agency is proposing that the labeling of corn and callus remover drug products formulated in a flammable vehicle, such as collodion, contain an appropriate flammability warning consistent with the requirements of 16 CFR Part 1500. (See comment 5 above.)

5. The agency is proposing to shorten and clarify the warnings for these products by combining, revising, or deleting a number of the Panel's recommended warnings. (See comments 1 and 6 through 8 above.) In addition, the agency is adding the statement "For external use only" to the warnings section. Use of this statement is consistent with a number of other OTC drug monographs for topical drug products. (See, for example, the tentative final monograph for OTC external analgesic drug products (February 8, 1983; 48 FR 5852); the tentative final monograph for OTC skin protectant drug products (February 15, 1983; 48 FR 6820); and the final monograph for OTC topical otic drug products (August 8, 1986; 51 FR 28656).)

6. The agency is proposing to revise the directions for use to delete references to using the product on the feet, soaking before treatment with the product, and encircling the corn or callus with petrolatum, and to revise the dosage regimen for products formulated in a collodion-like vehicle from once a day for no more than 14 days to once or twice daily as needed for up to 14 days. (See comment 9 above.)

7. In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs to substitute the word "doctor" for "physician" in OTC drug monographs on the basis that the word "doctor" is more commonly used and better understood by consumers. Based on comments received to these proposals, the agency has determined that final monographs and any applicable OTC drug regulation will give manufacturers the option of using either the word "physician" or the word "doctor." This tentative final monograph proposes that option. In addition, the agency is proposing to include the term "podiatrist" together with the term "doctor" throughout the labeling. (See comment 7 above.)

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule for OTC corn and callus remover drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act, Pub. L. 96–354. That assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC corn and callus remover drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invited public comment in the advance notice of proposed rulemaking regarding any impact that this rulemaking would have on OTC corn and callus remover drug products. No comments on economic impacts were received. Any comments on the agency's initial determination of the economic consequences of this proposed rulemaking should be submitted by June 22, 1987. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined that under 21 CFR 25.24(c)(6) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Interested persons may, on or before April 21, 1987, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on

the agency's economic impact determination may be submitted on or before June 22, 1987.

Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register**.

Interested persons, on or before February 20, 1988, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before April 20, 1988. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA–305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on April 20, 1988. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register**, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

List of Subjects in 21 CFR Part 358

Labeling, Over-the-counter drugs, Corn and callus remover drug products.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended by adding Part 358, consisting of 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); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

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

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

§358.503 Definitions.

As used in this subpart:

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

(b) *Collodion-like vehicle.* A solution containing pyroxylin (nitrocellulose) in an appropriate nonaqueous solvent that leaves a transparent cohesive film when applied to the skin in a thin layer.

(c) *Plaster vehicle.* A fabric, plastic, or other suitable backing material in which medication is usually incorporated for topical application to the skin.

§358.510 Corn and callus remover active ingredients.

The active ingredient of the product consists of any of the following when used within the specified concentration and in dosage form established for each ingredient:

(a) Salicylic acid 12 to 40 percent in a plaster vehicle.

(b) Salicylic acid 12 to 17.6 percent in a collodion-like vehicle.

§ 358.550 Labeling of corn and callus remover 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 a "corn and callus remover."

(b) *Indications.* The labeling of the product states, under the heading "indications," any of the phrases listed in this paragraph, as appropriate. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph (b), may also be used, as povided in § 330.1(c)(2), subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) "For the removal of corns and calluses."

(2) "Relieves pain by removing corns and calluses." This indication is permitted only in conjunction with the indication identified in paragraph (b)(1) of this section.

(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) "For external use only."

(ii) "Do not use this product if you are a diabetic or have poor blood circulation, except under the advice and supervision of a doctor or podiatrist."

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

(iv) "If discomfort persists, see your doctor or podiatrist."

(2) *For any product formulated in a flammable vehicle.* (i) The labeling should contain an appropriate flammability signal word, e.g., "extremely flammable," "flammable," "combustible," conisistent with 16 CFR 1500.3(b)(10).

(ii) "Keep away from fire or flame."

(3) *For any product formulated in a volatile vehicle.* "Cap bottle tightly and store at room temperature away from heat."

(4) *For any product formulated in a collodion-like vehicle.* (i) "If product gets into the eye, flush with water for 15 minutes."

(ii) "Avoid inhaling vapors."

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

(1) *For products containing salicylic acid identified in § 358.510(a).* "Wash affected area and dry thoroughly." (If appropriate: "Cut plaster to fit corn/callus.") "Apply medicated plaster. Repeat this procedure every 48 hours as needed (until corn/callus is removed) for up to 14 days."

(2) *For products containing salicylic acid identified in § 358.510(b).* "Wash

affected area and dry thoroughly. Apply one drop at a time to sufficiently cover each corn or callus. Let dry. Repeat this procedure once or twice daily as needed (until corn/callus is removed) for up to 14 days."

(e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this section.

Dated: December 6, 1986.

Frank E. Young,

Commissioner of Food and Drugs.

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