DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 358

[Docket No. 80N-0238]

RIN 0905-AA06

Wart Remover Drug Products for Over-the-Counter Human Use; Final Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing conditions under which over-the-counter (OTC) wart remover drug products are generally recognized as safe and effective and not misbranded. FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and all new data and information on wart remover drug products that have come to the agency's attention. This final monograph is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: August 14, 1990.

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

SUPPLEMENTARY INFORMATION: In the **Federal Register** of October 3, 1980 (45 FR 65609), 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 wart remover drug products, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products (Miscellaneous External Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by January 2, 1981. Reply comments in response to comments filed in the initial comment period could be submitted by February 2, 1981.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, after deletion of a small amount of trade secret information.

The agency's proposed regulation, in the form of a tentative final monograph, for OTC wart remover drug products was published in the **Federal Register** of September 3, 1982 (47 FR 39102). Interested persons were invited to file by November 2, 1982, written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal. Interested persons were invited to file comments on the agency's economic impact determination by July 27, 1987. New data could have been submitted until March 27, 1988, and comments on the new data until May 27, 1988.

In the **Federal Register** of March 27, 1987 (52 FR 9992), the agency issued a reproposal of the tentative final monograph for OTC wart remover drug products to reflect new data and information. The agency stated that data and comments submitted in response to the tentative final monograph for OTC wart remover drug products, published in the **Federal Register** of September 3, 1982 (47 FR 39102), had not yet been evaluated by the agency and that persons who previously submitted data and comments may wish to reevaluate them in light of the reproposed tentative final monograph. Accordingly, the agency stated that data and comments submitted in response to the reproposal as well as data and comments submitted in response to the tentative final monograph published in the **Federal Register** of September 3, 1982 (47 FR 39102), would be considered by the agency in establishing a final monograph. Interested persons were invited to file by May 26, 1987, written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the reproposal. Interested persons were invited to file comments on the agency's economic impact determination by July 27, 1987. New data could have been submitted until March 27, 1988, and comments on the new data until May 27, 1988. Final agency action occurs with the publication of this final monograph, which is a final rule establishing a monograph for OTC wart remover drug products. All data and comments described above are being addressed in this document.

The OTC drug procedural regulations (21 CFR 330.10) now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA is no longer using 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 is using instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III).

As discussed in the proposed regulation for OTC wart remover (52 FR 9992) drug products, the agency advised that the conditions under which the drug products that are subject to this monograph will be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication in the **Federal Register**. Therefore, on or after August 14, 1991, 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 response to the proposed rule on OTC wart remover drug products, four manufacturers and one medical professional submitted comments. No requests for oral hearing before the Commissioner were received. Copies of the comments received are on public display in the Dockets Management Branch. Any additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch (address above).

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notices 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 notice of proposed rulemaking. The volumes are on public

display in the Dockets Management Branch.

I. the Agency's Conclusions on the Comments

1. One comment applauded the reproposal of the tentative final monograph for its clarity, brevity, correctness, and the simple and reasonable definition for a "collodion-like" vehicle. The comment stated that clarification of this definition has been long needed. The comment concluded by saying that the proposed monograph in its present form is a paradigm of clear-thinking and careful rulemaking one likes to see coming from FDA.

2. One comment contended that OTC drug monographs are interpretive, as opposed to substantive, regulations. The comment referred to statements on this issue submitted earlier to other OTC drug rulemaking proceedings.

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products, published in the **Federal Register** of May 11, 1972 (37 FR 9464); in paragraph 3 of the preamble to the tentative final monograph for antacid drug products, published in the **Federal Register** of November 12, 1973 (38 FR 31260). FDA reaffirms the conclusions stated in those documents. Court decisions have confirmed the agency's authority to issue substantive regulations by rulemaking. (See, e.g., *National Nutritional Foods Association* v. *Weinberger*, 512 F.2d 688, 696–98 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers* v. *FDA*, 487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd*, 637 F.2d 887 (2d Cir. 1981).)

3. One comment expressed pleasure that the agency had expanded the concentration range and dosage form for salicylic acid to 12 to 40 percent in a plaster vehicle. Another comment supported the agency's Category I classification of salicylic acid at a 15-percent concentration in a plaster or collodion-like vehicle.

4. One comment stated that there were rumors that the combination of 16.7 percent salicylic acid and 16.7 percent lactic acid would be approved as a wart remover product for OTC human use. The comment contended that this would be a serious error because the potency of such a combination makes it necessary to restrict it to prescription use only.

After reviewing two studies that involved a combination product containing salicylic acid 16.7 percent and lactic acid 16.7 percent in flexible collodion and a third study that involved a combination product containing salicylic acid 5 percent and lactic acid 5 percent in flexible collodion, the Panel concluded that the lactic acid does not contribute greatly to the effectiveness of the combination and that salicylic acid is the active keratolytic ingredient (45 FR 65609 at 65617). The Miscellaneous External Panel placed this combination in Category III for effectiveness and concluded that data were needed to demonstrate that lactic acid contributes to the increased effectiveness of the combination over that of salicylic acid alone.

The agency agreed with the Panel's conclusions in the tentative final monograph for OTC wart remover drug products (47 FR 39102 at 39103). Following publication of that document on September 3, 1982, no additional data were received to support the combination of salicylic acid 5 to 17 percent and lactic acid 5 to 17 percent. Therefore, this combination is not included in the final monograph. (See also comment 8 below.)

5. One comment supported the reproposed tentative final monograph classification of 15 percent salicylic acid in a plaster or collodion-like vehicle as a Category I wart remover ingredient. The comment stated that its product, which contains 15 percent salicylic acid in a hydroscopic karaya gum pad with polypropylene backing, appears to comply with the reproposed monograph and should be marketable without new drug application (NDA) clearance. The product's labeling described the adhesive pad as being composed of natural nonsensitizing karaya, polyethylene glycol-300 U.S.P., propylene glycol U.S.P. and quaternium-15 and called the product a transdermal deliver system (Ref. 1).

The agency agrees that this product meets the definition of a plaster vehicle in § 358.103(c) of this final rule but finds that the product is not a transdermal delivery system. Transdermal delivery systems, such as those used to administer scopolamine, clonidine, estradiol, or nitroglycerin, are applied to the skin and the drug is absorbed continuously through the skin into the systematic circulation to provide therapeutic serum levels (Ref. 2). The comment's own labeling statements (e.g., the delivery systems provides for a more steady release of the drug into the stratum corneum, and the drug's activity appears to be due to a keratolytic action which results in mechanical removal of stratum corneum cells infected with the papilloma virus) argue against a transdermal designation because systemic absorption does not occur and the clinical effect is not a systemic one. The pharmacological activity results from a keratolytic action that leads to mechanical removal of stratum corneum cells infected with the papilloma virus in the same manner as other products subject to this rulemaking. After this comment was submitted, the company was informed (in a pending NDA for this product) that the reference to a transdermal wart removal system should not be included in the product's labeling (Ref. 3). Accordingly, it is not necessary to proceed with approval of the NDA. However, in order to be marketed OTC in accordance with this final monograph, the product must comply with these labeing provisions and not be labeled a transdermal delivery system. (See comment 13 below, for additional discussion of labeling.)

References

(1) Comment No. C00007, Docket No. 80N–0238, Dockets Management Branch.

(2) "Physicians' Desk Reference," 44th Edition, Medical Economics Company, Inc., Oradell, NJ, pp. 685–686, 853–856, 2042, 2070–2071, and 2181–2182, 1990.

(3) Letter from E. Tabor, FDA, to J. Neveaux, Minnetonka, Inc., dated March 7, 1988, included in OTC Volume 16CFM, Docket No. 80N–0238, Dockets Management Branch.

6. One comment asked about the future of a product containing 17 percent salicylic acid in a collodion-like vehicle that it claimed fits the definition of an OTC wart remover but is currently being marketed as a prescription product. Contending that advertisements for the product strongly suggest that it contains lactic acid as well as salicylic acid, the comment stated that marketing of this product has been particularly confusing for physicians.

The agency is aware that the product referred to by the comment is currently being marketed as a prescription product. However, there is no indication from the current or previous labeling (Refs. 1, 2, and 3) that this product also contains lactic acid. The agency is not aware of any advertisements that state or strongly suggest that the product contains lactic acid, and the comment did not provide any examples of advertisements to support its contention. The agency also is not aware that this product's marketing has been particularly confusing to physicians, and the comment did not provide any evidence to support its position.

Similar products can be marketed both prescription and OTC before a final monograph becomes effective. The agency will examine the labeling of this

product when the monograph becomes effective and determine the product's status at that point as part of normal compliance activity following establishment of a final monograph. Any necessary regulatory action will be considered at that time.

References

(1) "Physicians' Desk Reference," 44th Ed., Medical Economics Co., Inc., Oradell, NJ, pp. 998–999, 1990.

(2) "Physicians' Desk Reference," 43d Ed., Medical Economics Co., Inc., Oradell, NJ, p. 986, 1989.

(3) "Physicians' Desk Reference," 42d Ed., Medical Economics Co., Inc., Oradell, NJ, p. 897, 1988.

7. One manufacturer submitted new data on 17 percent salicylic acid in what it described as a polyacrylic film vehicle. The data are from a multicenter, double-blind, controlled clinical trial to evaluate the safety and effectiveness of 17 percent salicylic acid in this polyacrylic film vehicle versus the polyacrylic film vehicle without the active ingredient (Ref. 1). Subsequently, the manufacturer submitted additional information stating that the polyacrylic vehicle is already classified in Category I in the tentative final monograph (Ref. 2). The manufacturer explained that its vehicle contained pyroxylin (nitrocellulose), volatile solvents (alcohol and toluene), and a plasticizer (acrylates copolymer), and the vehicle meets the description of flexible collodion contained in the Miscellaneous External Panel's report (45 FR 65609 at 65612). The manufacturer added that all ingredients but one (polyester resin) are listed in the Cosmetic, Toiletry and Fragrance Association's Cosmetic Ingredient Dictionary, and that polyester resin is composed of trimellitic anhydride, adipic acid, neopentyl glycol, and cyclohexane dimethanol 70 percent in normal butyl acetate. The manufacturer also stated that polyester resin is a component of a number of widely used commercially available nail polishes (Ref. 3).

Subsequently, additional data were obtained for a total of 62 subjects, of which 59 were acceptable for efficacy evaluation (Refs. 1 and 4). Subjects were divided on a random basis to either the active treatment group (30 subjects) or the vehicle treatment group (29 subjects). Treatments were blinded to both the subjects and investigators. The subjects were instructed to soak each wart with warm water for at least 5 minutes, to dry the area thoroughly, and then paint the surface of the wart. Subjects were advised to discontinue use if excessive irritation occurred. At the initial visit, a description of each wart's location, size, and thickness was made. At each follow-up visit (weeks 2 and 3), the size and thickness of each wart were determined and compared to baseline values. Additionally, at each follow-up visit, each wart's response to medication was assessed as cured, resolving, same (failures), or worse. For the 30 subjects who received active drug treatment for 3 weeks, 9 (30 percent) were rated as cured, 12 (40 percent) were rated as resolving, 9 (30 percent) were rated as same, and 0 were rated as worse. For the 29 subjects who received placebo for 3 weeks, 1 (3 percent) was rated as cured, 4 (14 percent) were rated as resolving, 23 (79 percent) was rated as same, and 1 (3 percent) was rated as worse. Differences in mean wart areas from baseline to week 3 were not statistically significant, but differences in mean wart thicknesses was statistically signficant for the active medication group ($p < 0.01$).

None of the subjects experienced an adverse reaction severe enough to be taken out of the study. Only 3 adverse reactions were reported—all in the active medication group. One subject manifested red and raw areas of a mild degree surrounding treated warts, which lasted for 2 days. Another subject was being treated for five warts, one of which kept breaking open during therapy and manifested a moderate amount of bleeding for 3 to 4 days. The investigator reported that this reaction had an unknown etiology, but discontinued treating that one wart. The third subject complained of a mild burning and itching in interdigital areas for about 15 minutes during 1 day of treatment. Etiology was unknown and study medication was continued.

The agency has evaluated the manufacturer's vehicle described above and determined that it meets the definition of a "collodion-like vehicle" included in § 358.103(b) of this final monograph. The Panel designated collodion as the vehicle for liquid wart remover drug products containing salicylic acid (45 FR 65609 at 65618). Collodion is an official article in the United States Pharmacopeia (U.S.P.) (Ref. 5). The Panel noted that salicylic acid used in the treatment of warts is usually formulated in flexible collodion, which contains pyroxylin (a nitrocellulose derivative), volatile solvents (ether, acetone, or alcohol), and plasticizers (camphor and castor oil) (45 FR 65612). Flexible collodion is also an official article in the U.S.P. (Ref. 5).

In the tentative final monograph for OTC corn and callus remover drug products, the agency noted that, in addition to collodion and flexible collodion, some formulations contain other inactive ingredients or varying amounts of solvent which provide for increased spreadability and increased pliability of the product after it dries on the skin (52 FR 5412 at 5414). The agency proposed the term "collodion-like" instead of "collodion" in specifying the vehicle for liquid formulations containing salicylic acid and defined "collodion-like" 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." The agency also proposed this same definition for salicylic acid used in liquid formulations as OTC wart remover drug products (52 FR 9992 at 9993).

The manufacturer's vehicle in the salicylic acid product used in the clinical trial described above contains pyroxylin (nitrocellulose) in a nonaqueous solvent that leaves a transparent cohensive film when applied to the skin. The vehicle also contains a plasticizer as does flexible collodion. The agency has determined that the clinical trial described above shows that salicylic acid in this vehicle is effective and the vehilce does not cause adverse reactions that would cause it to be considered unsafe. Further, the vehicle is a common nail polish formulation (Refs. 3 and 6), which the agency considers to be safe. Thus, the agency concludes that 17 percent salicylic acid in the manufacturer's vehicle is generally recognized as safe and effective as an OTC wart remover drug product when labeled according to the conditions of this final monograph.

References

(1) Comment No. RPT, Docket No. 80N–0238, Dockets Management Branch.

(2) Comment No. C00003, Docket No. 80N–0238, Dockets Management Branch.

(3) Formulation for Nail Polish Tevco Vehicle #32403, identified as Exhibit #25d, February 26, 1985, included in OTC Volume 16CFM, Docket No. 80N–0238, Dockets Management Branch.

(4) "Supplemental Efficacy Data for Study 83–07" identified as Exhibit #21, dated February 26, 1985, included in OTC Volume 16CFM, Docket No. 80N–0238, Dockets Management Branch.

(5) "United States Pharmacopeia XXII—National Formulary XVII," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 353, 1989.

(6) Memorandum of Telephone Conversation between K. Freeman, FDA, and J. Wenninger, FDA, is included in OTC Volume 16CFM, Docket No. 80N–0238, Dockets Management Branch.

8. One comment requested that lactic acid be considered an inactive

ingredient rather than as an active ingredient in OTC wart remover drug products. The comment asked that § 358.110 of the tentative final monograph be rewritten to include the phrase "or in a lactic acid collodion vehicle" as follows: "The active ingredient and its concentration in the product is as follows: salicylic acid 5 to 17 percent in a collodion vehicle or in a lactic acid collodion vehicle." Alternatively, the comment requested that the phrase "in a collodion vehicle" not be included in § 358.110 of the final monograph.

The comment contended that "lactic acid (5 to 17 percent) when added to salicylic acid (5 to 17 percent) in a collodion base results in a drug formulation of better quality than the same formulation without the salicylic acid." The comment explained that a topical collodion vehicle containing a therapeutically active ingredient must have three primary characteristics: (1) Act as a protective agent to the drug, (2) adhere to the skin after its solvent has evaporated, and (3) retain a residual nonvolatile liquid content sufficient to enable the active ingredient to retain enough solubility to permit molecular transfer into the skin. The comment further explained that when salicylic acid alone is dissolved in flexible collodion and applied to the skin, a dry film is created as a result of evaporation, causing poor adhesion of the salicylic acid as well as inefficient drug mobility. The comment stated that it has found that including 15 to 20 percent lactic acid in the product will overcome these deficiencies because lactic acid satisfies the following criteria: (1) Its oil/water solubility characteristics permit improved adhesion of the drug to the skin, and (2) lactic acid does not evaporate from the film. The comment also stated that the solubility of salicylic acid in lactic acid is 3 percent, so that the lactic acid remains saturated with salicylic acid throughout the treatment period, with sufficient solubility for efficient molecular transfer into the skin.

In further support of lactic acid's enhancement of adhesion of salicylic acid in collodion, the comment cited an unpublished in-vitro study carried out with salicylic acid collodion preparations containing 16.7 percent salicylic acid and varying amounts of lactic acid in order to demonstrate the concentration of lactic acid which would be most beneficial to the finished product (Ref. 1). Based on visual evaluation of adhesion properties, 15 percent lactic acid provided the best adhesive characteristics with a coherent film on the walls of the glass tubes. Concentrations of lactic acid ranging from 0 to 10 percent and from 20 to 25 percent were rated for adhesion as either nil or slight (Ref. 1).

The comment stated that its product contains salicylic acid and lactic acid 16.7 percent each, and flexible collodion 66.6 percent in order to obtain a 1:1:4 weight-to-weight ratio of the acids in the flexible collodion. The comment asserted that lactic acid's safety has been clearly established, citing the Miscellaneous External Panel's report (45 FR 65609 at 65615; October 3, 1980) and the tentative final monograph on OTC wart remover drug products (47 FR 39102 at 39103; September 3, 1982) as support.

The comment stated that the use of lactic acid as an inactive ingredient is in accord with 21 CFR 330.1(e), which provides that monograph products may contain only those suitable inactive ingredients which are safe in the amounts administered and which do not interfere with the preparation's effectiveness or with suitable tests or assays to determine if a drug meets its professed standards. The comment mentioned that salicylic and lactic acids can be quantified separately in the same formulation; thus, there is no interaction between them. The comment added that the Panel concluded from the Bunney study (Ref. 2) that salicylic acid rather than lactic acid is responsible for effectiveness and that lactic acid is not interfering with the salicylic acid when enhancing the formulation's pharmaceutical qualities (45 FR 65609 at 65617).

The comment further contended that neither the Panel nor FDA considered whether lactic acid was a suitable inactive ingredient in wart removal drug products and that there was no reason to do so because the OTC drug review is concerned almost exclusively with active ingredients. The comment noted that lactic acid was reviewed as an active ingredient.

The comment cited as precedent an agency letter (Ref. 3) notifying another manufacturer that oil of turpentine could be included as an inactive ingredient for organoleptic reasons in an antitussive drug product when oil of turpentine had been classified in Category III as an antitussive active ingredient.

The comment contended that if the tentative final monograph for OTC wart remover drug products had not specified the inactive ingredient, i.e., in a collodion vehicle, for wart remover drug products, lactic acid could have been included as an inactive ingredient in a wart removal drug product without the necessity of obtaining a modification of the monograph. The comment claimed that the tentative final monograph as presently written would permit the inclusion of lactic acid along with the collodion as a suitable inactive ingredient pursuant to 21 CFR 330.1(e). However, in order to remove any ambiguity with regard to the issue, the comment urged that the tentative final monograph be amended to include lactic acid as an inactive ingredient or, in the alternative, that no inactive ingredients be specified.

The agency disagrees with the comment's requests. The Panel reviewed lactic acid as an active ingredient in OTC wart remover drug products (45 FR 65609 at 65615). The comment's statement about the Panel's conclusions from the Bunney study (Ref. 2) is out of context. The Panel stated it could find no data on the use of lactic acid alone in the treatment of warts, and that data showing that lactic acid contributes to the increased effectiveness of the combination over that of salicylic acid alone are needed to upgrade the combination to Category I (45 FR 65617). When the Panel concluded that lactic acid does not contribute greatly to the combination's effectiveness, it did not regard lactic acid as an inactive ingredient but as an ingredient for which no data were found to support its use as a wart remover.

The Panel mentioned a study by Van Scott and Yu (Ref. 4), which stated that lactic acid is one of a group of compounds that modify keratinization in ichthyosis. Histologically, preparations of biopsy specimens taken from treated and untreated skin reveal distinct changes that suggest that these compounds may cause an immediate effect on epidermis keratinization. One change that occurs is abrupt loss of the entire stratum corneum. This is seen clinically by sudden separation of thick scales to reveal a normal skin surface. Another change noted in this study is that significant shedding occurs, reducing the thickness of the epidermis (45 FR 65610). These microscopic and clinical changes attributable to lactic acid clearly fall within the statutory definition of the effects produced by a drug. The act defines a "drug" in part as an article "intended to affect the structure or function of the body" (21 U.S.C. 321(g)(1)(C)). Another submission (Ref. 5) supporting the use of 5 percent lactic acid in combination with salicylic acid described lactic acid as being a caustic agent, having keratoylic activity, and as having corrosive properties. The study by Van Scott and Yu and the submission (Ref. 5) clearly indicate that

lactic acid is an active ingredient, i.e., a drug, when used in these types of products.

The comment presently markets a prescription wart remover drug product containing salicylic acid 16.7 percent and lactic acid 16.7 percent as active ingredients in a collodion vehicle (Ref. 6). Product labeling states that its pharmacologic activity is generally attributed to the keratolytic action of both lactic acid and salicylic acid (Ref. 6). Another company also markets a product containing the same active ingredients in the same concentration with the same labeling statement of pharmacologic activity (Ref. 7). Lactic acid 16.7 percent cannot be an inactive OTC ingredient and also be an active ingredient at the same concentration in similar products.

The agency regards lactic acid to be an active ingredient in products labeled for the removal of warts and is not including lactic acid in the final monograph as an optional inactive ingredient as suggested by the comment because of a lack of data demonstrating its effectiveness. Further, in a proposed rule on inactive ingredients (April 12, 1977; 42 FR 19156 at 19157), the agency stated the following:

> Various OTC drug panels have questioned whether an OTC drug may retain as an inactive ingredient an ingredient that was formerly listed as an active ingredient, but which was found not to be generally recognized as safe and effective (Category II) or to require additional testing (Category III). If these ingredients have been promoted by manufacturers for an extended time, there is a potential for misleading consumers if the general recognition of the safety and effectiveness issue is unresolved and the name of the ingredient is retained on the label or in the labeling with an unwarranted degree of prominence. The Commissioner believes this should not be permitted, and this proposal is intended to preclude the retention and redesignation of an active ingredient as an inactive ingredient unless it serves an acceptable function as an inactive ingredient. As a result, manufacturers of OTC drug products containing an ingredient in Category II or Category III shall, at the end of the time period permitted for marketing, or if found to require further testing before a determination as to general recognition of safety and effectiveness can be made for such ingredients, be required by the effective date either to reformulate the product to remove the ingredient or if it is retained in the product as an inactive ingredient, to establish that the ingredient fulfills the requirements for use as an inactive ingredient in the product.

If lactic acid is retained in a wart remover drug product as an inactive ingredient, the manufacturer must establish that lactic acid fulfills the requirements for use as an inactive ingredient. The intended uses of lactic acid, as the comment stated, are as a protective agent to the drug, as an adherent to the skin after the solvent has evaporated, and as a retentive of residual nonvolatile liquid sufficient to retain enough solubility to permit molecular transfer into the skin. The physical characteristic of adhesion of various concentrations of lactic acid is reported in the comment's description of an unpublished in-vitro study's results (Ref. 1). The agency cannot use the comment's description of the study as the sole basis to determine the inactive ingredient status of lactic acid nor can the agency ignore the keratolytic activity of lactic acid, as noted above. Despite the comment's contention that lactic acid is a protective and adherent, lactic acid is still an active ingredient that has not been shown to produce an effective level of keratolysis sufficient to be included in this final monograph. Furthermore, the agency's proposed rule on inactive ingredients lists a number of uses of inactive ingredients (42 FR 19156 at 19160). It does not include the protective and adherent uses of lactic acid as the comment described. It does include under proposed § 330.3(p) "solvents and vehicles": "Substances used to dissolve or extract another substance or used as carriers of other substances." However, the agency considers that mechanism as being different from retaining a residual nonvolatile liquid, as mentioned by the comment. Therefore, the agency does not consider lactic acid an inactive ingredient for any use listed in its proposal at 42 FR 19160.

With regard to the comment's argument about the dual status of oil of turpentine, data were submitted to the Cough-Cold Panel on the use of oil of turpentine as an active antitussive ingredient combined with menthol, camphor, eucalyptus oil, thymol, and myristica oil in a petrolatum ointment base for application to the chest. Based on submitted data, in the final monograph for OTC antitussive drug products (52 FR 30042 at 30054; August 12, 1987), the agency made a final determination that oil of turpentine was a nonmonograph active ingredient. Publication of the final monograph superseded the agency's letter of February 16, 1983 (Ref. 3) discussing oil of turpentine. In addition, in the tentative final monograph on cough, cold, allergy, bronchodilator, and antiasthmatic combination drug products (53 FR 30522 at 30547; August 12, 1988), the agency determined that oil of turpentine at 4.5 percent was an active ingredient but classified thymol 0.1 percent, cedarleaf oil 0.38 percent, and myristica oil 0.485 percent as inactive ingredients because of their low concentrations. Menthol 2.6 percent, camphor 4.7 percent, and eucalyptus oil 1.2 percent, were considered active ingredients (53 FR 30547). Although oil of turpentine in a combination is still pending further proceedings in the cough-cold combinations rulemaking, the agency considers the status of oil of turpentine an active ingredient, and the agency's position on that ingredient does not support the comment's argument that lactic acid is an inactive ingredient.

For the reasons stated above, the agency is classifying lactic acid (5 to 17 percent) a nonmonograph active ingredient in this final rule.

References

(1) Comment No. C00002, description of unpublished in-vitro study by Dermal Laboratories, Ltd., pp. 3–4, Docket No. 80N–0236, Dockets Management Branch.

(2) Bunney, M.H., M.W. Nolan, and D.A. Williams, "An Assessment of Methods of Treating Viral Warts by Comparative Treatment Trials Based on a Standard Design," British Journal of Dermatology, 94:667–679, 1976.

(3) Letter from W.E. Gilbertson, FDA to G.F. Hoffnagle, Richardson-Vicks, Inc., coded ANS 1, Docket No. 76N–052T, Dockets Management Branch.

(4) Van Scott, E.J., and R.J. Yu, "Control and Keratinization with a-Hydroxy Acids and Related Compounds. Topical Treatment of Ichthyotic Disorders," Archives of Dermatology, 110:586–590, 1974.

(5) OTC Volume 160359, pp. 5, 59, and 60.

(6) "Physicians' Desk Reference," 43d Ed., Medical Economics Co., Inc., Oradell, NJ, p. 621, 1989.

(7) "Physicians' Desk Reference," 44th Ed., Medical Economics Co., Inc., Oradell, NJ, p. 2163, 1990.

9. One comment urged the agency to consider requiring a package insert for OTC wart remover drug products that would clearly describe, in layman's terms, the type of warts on which the drug could be used, a simple explanation of how the drug works, how it should be used, the potential side effects, and the precautions and contraindications, especially for the elderly. The comment did not feel that the labeling proposed in § 358.150 was sufficient for the lay population to safely and effectively self-medicate with these products. Noting that salicylic acid is "not without side effects or risks," the comment was specifically concerned about risks in the elderly population because of the higher incidence of diabetes mellitus, peripheral vascular disease, and decreased visual acuity.

The agency appreciates the comment's concern, but does not believe

that it is necessary to require a package insert for OTC wart remover drug products. The agency is aware that the Miscellaneous External Panel considered self-medication by the elderly with OTC wart remover drug products and, accordingly, proposed certain warnings, which the agency has adopted. These warnings address several of the concerns raised by the comment. The Panel recommended the following warning "Do not use if you are a diabetic or have poor blood circulation because serious complications may result." (See 45 FR 65609 at 65618.) The agency concurred with this recommendation in the tentative final monograph 47 FR 39102 at 39104 and in the reproposed tentative final monograph (52 FR 9992 at 9993). However, in this document the warning has been revised and is included in § 358.150(c)(1)(ii) of this final monograph. See comment 11 below.

The Panel noted that systemic absorption of salicylates occurs whether the salicylates are administered orally, rectally, intravenously, or cutaneously (through the skin) (45 FR 65609 at 65612). However, the Panel stated that it was unaware of any report of salicylism (toxic reaction) occurring from the cutaneous use of salicylic acid as a wart remover. The agency also is not aware of any such reports. Therefore, the agency concludes that the labeling information required by § 358.150 of this final monograph should provide for the safe and effective use of OTC wart remover drug products by all populations, including the elderly.

The agency is aware that wart remover drug products are marketed in small containers and that it is difficult to print all of the required labeling information on the immediate container label in a print size that can readily be read by elderly consumers. The agency encourages manufacturers of these products to provide a consumer package insert or outer container that provides a larger size print for all consumers, particularly for the elderly. The agency has no objection if manufacturers provide additional information of the type requested by the comment in addition to the required monograph labeling. Manufacturers are also encouraged to print a statement on the product container label, carton, or package insert suggesting that the consumer retain the carton or package insert for complete information about the use of the product when all the required labeling does not appear on the product container label.

10. One comment recommended that the definition of "collodion-like vehicle" in proposed § 358.103 be slightly modified to read as follows: "A solution containing pyroxylin or film-forming vehicle in an appropriate solvent that leaves a transparent cohesive film when applied to the skin in a thin layer." The comment contended that this proposed definition would clarify that "any appropriate vehicle similar to a collodion (*e.g.*, collodion-like) would be acceptable," and that this flexibility of choice of vehicles allows for scientific improvement and refinement beyond the vehicles commonly used today, without necessitating amendment of a final monograph. The comment added that its request comports with the agency's rationale for expanding the definition from "collodion" to "collodion-like" (52 FR 9992 at 9993) and is consistent with the broad definition the agency gave to "plaster vehicle," which allows for improved topical patches utilizing technologies beyond those specifically in use today.

While the agency has tried to be flexible in the monograph definitions to allow for reasonable product improvement and innovation, it does not agree with the comment's proposed modification of the definition of a collodion-like vehicle. Addition of the words "film-forming vehicle" in the definition would make the definition too broad, would expand the definition beyond vehicles that are similar to collodion, and could allow any "film-forming vehicle" to be used. If this occurred, it could result in the introduction into the market of a wide variety of natural and synthetic film-forming compounds whose impact on the safety and effectiveness of salicylic acid is unproven. It is possible that such compounds could eventually be included in the final monograph, but data would be needed to support their interaction with salicylic acid used in wart remover drug products. Accordingly, the agency is not revising the definition of "collodion-like vehicle" in § 358.103 at this time, but will consider doing so in the future if vehicles of the type requested by the comment are found to be acceptable for inclusion in the monograph.

11. One comment suggested "a slight variation" to the warning proposed in § 358.150(c)(1)(ii), to read as follows: "Do not use if you are diabetic or have poor circulation or if there is any inflammation or irritation of the affected area." The comment stated that this proposed revision is preferable because it combines the warnings in § 358.150(c)(1) (ii) and (iii) and is stronger in its exhortation against use by diabetics and those with poor circulation. The comment contended that advising diabetics against the use of salicylic acid is medically sound and standard physician practice. The comment concluded that, for medical and product liability reasons, it would prefer to retain its label warning (suggested above) that it has used in recent years on its wart remover drug products. The comment did not include any documentation in support of the more stringent, combined warning.

The agency notes that the comment's suggestion involves more than the combining of two warnings. The warning against use by diabetics that the agency proposed in the tentative final monograph reads 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." The other warning proposed by the agency in the tentative final monograph reads as follows: "Do not use on irritated skin or on any area that is infected or reddened." The first warning to "diabetics" allows use of the product under a doctor's supervision. The second warning describes a "do not use" condition and is not dependent on advice or supervision by a doctor. The warning suggested by the comment would eliminate use of the product by a diabetic even under a doctor's supervision.

The Panel, in its review of keratolytics (chemical agents used to treat warts), considered the safety issues concerning the use of salicylic acid by diabetics and those individuals having poor blood circulation. After reviewing the data available at that time, and considering its members' experience, the Panel stated (45 FR 65609 at 65611):

> However, persons with poor circulation or diabetes should not use OTC preparations for removing warts except on the advice and under the supervision of a doctor. The Panel feels that such individuals are more prone to infections which may result from injury to surrounding skin by the OTC preparation or by mechanical attempts to remove the wart.

In evaluating the comment's suggestion, the agency reviewed a number of commonly used reference books (Refs. 1 through 4) but found that the references do not support the comment's contention that diabetics and individuals with poor circulation absolutely should not use wart remover drug products. For example, Basic & Clinical Pharmacology mentions that "Particular care must be exercised when using the drug on the extremities of diabetics or patients with peripheral vascular disease," (Ref. 1). Drug Evaluations (Ref. 2) states that caution must be exercised when a 40-percent

plaster is used, particularly on the extremities, in diabetics, or in patients with peripheral vascular disease, "since acute inflammation and ulceration may occur after excessive use." The United States Dispensatory (Ref. 3) states that plasters containing 40 percent of salicylic acid may cause acute inflammation and ulceration in diabetics or in persons with peripheral vascular disease "if not used with caution." Drug Information for the Health Care Provider (Ref. 4), in its discussion of the topical use of salicylic acid, states that products containing 25 percent or more of salicylic acid are not recommended for use on inflamed skin * * * or in individuals with diabetes or circulatory failure (impairment) since acute inflammation or ulceration may occur.

In discussing factors that lead to tissue necrosis in the diabetic foot, Edmonds (Ref. 5) states that "chemical trauma can result from the use of keratolytic agents such as 'corn plasters.' They often contain salicylic acid which causes ulceration in the diabetic foot." In providing general advice on foot care for the "at risk" diabetic patient, Boulton (Ref. 6) states "Do not use chemical agents (keratolytics) to treat calluses or corns."

The agency also reviewed the labeling for keratolytic drug products containing salicylic acid that appears in the Physician's Desk Reference for Nonprescription Drugs (Ref. 7) and found that the labeling for the listed wart remover drug products contain a warning that the product is not recommended for use by diabetics or individuals with impaired or poor blood circulation.

Based on the above, the agency has determined that there is adequate support for a stronger warning, as requested by the comment. In addition, based on the serious consequences that can result from misuse, the agency believes it is better to err on the side of caution and to have the labeling of these OTC drug products state that the product should not be used under certain conditions rather than state an "except under" condition for use. Therefore, the agency is agreeing with the comment's suggested approach to combine the warnings in § 358.150(c) (ii) and (iii) but is revising its recommended warning slightly for clarity. The revised warning appears in § 358.150(c)(1)(ii) of this final monograph as follows: "Do not use this product on irritated skin, on any area that is infected or reddened, if you are a diabetic, or if you have poor blood circulation." This revised warning now contains the same information as the warning proposed in § 358.150(c)(1)(iii), and that warning is not included in this final monograph. Accordingly, the warnings in paragraphs (c)(1) (iv) and (v) are redesignated as (iii) and (iv) in this final monograph.

References

(1) Katzung, B.G., editor, "Dermatologic Pharmacology," in "Basic & Clinical Pharmacology," 2d Ed., Lange Medical Publications, Los Altos, CA, p. 768, 1984.

(2) "Antiviral Agents for Warts and Molluscum Contagiosum," in "Drug Evaluations," 6th Ed., American Medical Association, Chicago, p. 1518, 1986.

(3) Osol, A., R. Pratt, and A.R. Gennaro, "The United States Dispensatory," 27th Ed., J.B. Lippincott Co., Philadelphia, p. 1035, 1973.

(4) "Salicyclic Acid (Topical)," in "Drug Information for the Health Care Provider", 5th Ed., Mack Printing Co., Easton, PA, p. 1121, 1985.

(5) Edmonds, M.E., "The Diabetic Foot: Pathophysiology and Treatment," Clinics in Endocrinology and Metabolism, 15:897, 1986.

(6) Boulton, A.J.M., "The Diabetic Foot," The Medical Clinics of North America, 72:1520, 1988.

(7) "Physician's Desk Reference for Nonprescription Drugs," 11th Ed., Medical Economics Co., Inc., Oradell, NJ, pp. 587 and 747, 1990.

12. One comment stated that the directions for use of most currently marketed wart remover drug products containing salicylic acid suggest that the user soak the area before application of the product. Noting that it has no data that soaking is mandatory, the comment requested that "permissive soaking" be allowed in the directions and suggested the following language be included in § 358.150(d):

(1) *For products containing salicylic acid identified in § 358.110(a).* "Wash affected area (soaking wart for several minutes, if desired) before drying thoroughly." (If appropriate: "Cut plaster to fit wart.") "Apply medicated plaster. Repeat procedure every 48 hours as needed (until wart is removed) for up to 12 weeks."

(2) *For products containing salicylic acid identified in § 358.110(b).* "Wash affected area (soaking wart for several minutes, if desired) before drying thoroughly." Apply one drop at a time to sufficiently cover each wart. Let dry. Repeat this procedure once or twice daily as needed (until wart is removed) for up to 12 weeks."

Another comment addressed the directions included in § 358.150(d) of the first tentative final monograph on OTC wart remover drug products (47 FR 39102 at 39104 to 39105). These directions included soaking the wart for 5 minutes before applying the salicylic acid product. The comment contended that this procedure is unnecessary because any product containing salicylic acid as a keratolytic would be effective without soaking. The comment requested that the sentence "Wash affected area and soak wart for 5 minutes" be deleted from the directions.

The agency has reviewed the Panel's discussion of wart remover drug products and notes that the Panel stated that "the therapeutic effectiveness of salicylic acid in wart therapy depends upon the presence of moisture; therefore, salicylic acid is usually incorporated into vehicles (plasters, flexible collodions, occlusive ointments) that occlude the area and promote hydration (taking up of water), causing maceration of the skin" (45 FR 65609 at 65612). Although the Panel did not discuss whether test subjects did or did not soak the affected area before applying the wart remover product containing salicylic acid , it did include soaking of the wart for 5 minutes before application of the product as part of its recommended directions (45 FR 65609 at 65613).

In the tentative final monograph for OTC corn and callus remover drug products, published in the Federal Register of February 20, 1987 (52 FR 5412), the agency reviewed the results of a double-blind placebo-controlled study in which the effect of soaking as a means of increasing efficacy of salicylic acid in removing soft corns was evaluated (Ref. 1). At that time, the agency determined that it was unnecessary to soak the affected area and revised the previously-proposed directions to eliminate "soaking" (52 FR 5416). The agency has re-evaluated this study and determined that it did not include a "non-soaking" group, but that all test subjects soaked the corn for 5 minutes before applying the medication and soaked for either 5 minutes or 15 minutes before attempting removal of the corn. Although this study did not show that soaking 5 minutes prior to applying the salicylic acid is necessary for salicylic acid to be effective, it also did not show that any adverse effects occur if the corn is soaked before the area is dried and the corn remover product applied. The agency notes that although this study was conducted on soft corns, the same findings are relevant to the removal of hard corns/calluses and warts because the category I active ingredient, salicylic acid, and its mode of action, keratolysis, are the same for all three conditions. It is possible that soaking increases the presence of moisture in the corn or wart, which then may promote hydration and aid the therapeutic effectiveness of salicylic acid, as the Panel indicated.

The agency has examined the directions for use for a number of currently marketed wart remover drug products and notes that some include soaking the wart for varied periods of time ranging from several minutes up to 30 minutes before the product is applied. Some of the products include directions to soak in hot water and some say to use warm water, while others do not specify temperature (Refs. 2 and 3).

There is no evidence that using different soaking times or temperatures is likely to alter the effectiveness of the wart remover drug products. The agency believes that while hot water may cause burns, warm or cold water could be used effectively for soaking but that warm water would be more comfortable. Based on the panel's recommendation, the agency's re-evaluation of the study discussed above, and on the historical and current use of wart remover drug products, the agency is including soaking of the wart in warm water for 5 minutes before application of the salicylic acid as an optional direction for those manufacturers who wish to give consumers the option to do so. Accordingly, the agency is revising § 358.150(d) in this final monograph to read as follows:

(1) *For products containing salicylic acid identified in § 358.110(a).* "Wash affected area." (optional: "May soak wart in warm water for 5 minutes.") "Dry area thoroughly." (If appropriate: "Cut plaster to fit wart.") "Apply medicated plaster. Repeat procedure every 48 hours as needed (until wart is removed) for up to 12 weeks."

(2) *For products containing salicylic acid identified in § 358.110(b).* "Wash affected area." (optional: "May soak wart in warm water for 5 minutes.") "Dry area thoroughly. Apply one drop at a time to sufficiently cover each wart. Let dry. Repeat this procedure once or twice daily as needed (until wart is removed) for up to 12 weeks."

References

(1) Goodman, J.J., and L. Farris, "Evaluation of Safety and Effectiveness 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.

(2) "Physicians' Desk reference for Nonprescription drugs," 11th Ed., Medical Economics Co., Oradell, NJ, pp. 567 and 747, 1990.

(3) Labels for currently marketed wart remover drug products included in OTC Volume 16PFM, Docket No. 80N–0238, Dockets Management Branch.

13. One comment suggested three modifications to the directions proposed in § 358.150(d)(1) for wart remover drug products in a plaster vehicle to accommodate its salicylic acid product in an adhesive pad delivery system. (See comment 5 above.) The comment requested the following additions (italicized) to the proposed directions: "Wash affected area and dry thoroughly." (If appropriate: "Cut plaster *material* to fit wart.") "Apply medicated plaster *as directed.* Repeat procedure every *24 to 48* hours as needed (until wart is removed) for up to 12 weeks."

The agency notes that the definition of "plaster vehicle" in this final monograph refers to a "fabric, plastic, or other suitable backing material * * *." Accordingly, adding the word "material" after the word "plaster," as suggested by the comment, would provide no additional useful information to the user of the product.

The agency also does not see any benefit to adding the words "as directed," as suggested by the comment, because these OTC drug products are intended for self-diagnosis and treatment and are not dependent on the receipt of directions from a doctor. If there are any special directions that relate to using a particular product, then such information should appear as part of the manufacturer's additional directions for the product. The monograph provides the minimum directions necessary for use of the product. Manufacturers may supplement these directions with additional information necessary to use their specific product. For example, the agency notes that the manufacturer's directions for its specific product include statements to "keep plastic film on the top of pad facing up and to apply sticky bottom side to the wart." The agency finds no need to incude such directions in this final monograph; however, manufacturers may add such information, as appropriate, to the labeling of their products.

Neither the Miscellaneous External Panel's report (45 FR 65609) nor the first tentative final monograph for OTC wart remover drug products (47 FR 39102) included salicylic acid in a plaster vehicle. The directions for salicylic acid in a plaster vehicle that were included in the reproposed tentative final monograph for OTC wart remover drug products were based upon data and comments submitted to the rulemaking for OTC corn/callus remover drug products (52 FR 9992). In developing those directions, the agency recognized that, although the etiology and pathology of corns and calluses are different from that of warts, the Category I active ingredient, salicylic acid, and its mode of action, keratolysis, are common to both rulemakings (52 FR 9992). The studies that supported the effectiveness of 40 percent salicylic acid in a plaster vehicle for the treatment of corns and calluses utilized a 48-hour treatment interval (47 FR 526).

The comment submitted data from three double-blind, placebo controlled clinical studies (Ref. 1). The purpose of two of the studies was to investigate the efficacy of 5 percent and 15 percent concentrations of salicylic acid in the treatment of common warts when administered in a karaya gum, glycol patch. The control patch was a polymer of karaya gum plus glycols without the salicylic acid. The amount of the glycols was increased to compensate for the missing salicylic acid. The treatment period of the studies was 12 weeks, with dermatologist evaluation at weeks 2, 4, 6, 8, and 12. Subjects were directed to apply the patch at bedtime, to leave it on at least 8 hours, and remove and discard the patch in the morning. Treatments were repeated daily. The same protocol was used at studies at two sites; 66 subjects completed one study, and 52 subjects completed the other study. No subjects were dropped from either study because of adverse reactions. The agency concluded that only one of the studies showed superiority in both the number of subjects cured and the number of warts cured. The other study indicated that, for warts cured, the 15 percent concentration of salicylic acid was not statistically different from placebo. The third study evaluated only the 15 percent concentration of salicylic acid versus its karaya gum glycol placebo vehicle. A total of 61 subjects entered the study, but 8 were excluded from evaluation for compliance reasons. Subjects again applied the treatments for 8 hours at bedtime on a daily basis. Warts were evaluated at 4, 8, and 12 weeks. The data indicate that the product is superior to placebo in the treatment of warts (Ref. 1).

Based on the above, the agency is adding this formulation to the final monograph by revising proposed § 358.110 to add paragraph (c) for the active ingredient, "Salicylic acid 15 percent in a karaya gum, glycol plaster vehicle." The agency is also revising proposed § 358.110 to add a new paragraph (d)(3) as folllows: *"For products containing salicylic acid identified in § 358.110(c).* 'Wash affected area.' (Optional: 'May soak wart in warm water for 5 minutes.') 'Dry area thoroughly.' (If appropriate: 'Cut plaster to fit wart.') "Apply medicated plaster at bedtime, leave in place for at least 8 hours; in the morning, remove plaster and discard. Repeat procedure every 24

hours as needed (until wart is removed) for up to 12 weeks.' "

Reference

(1) Comment No. RFT 2, Docket No. 80N-0238, Dockets Management Branch.

14. One comment noted its continuing position that FDA cannot legally and should not, as a matter of policy, prescribe exclusive lists of terms from which indications for use for OTC drug products must be drawn and prohibit alternative OTC drug labeling terminology to describe such indications which is truthful, not misleading, and intelligible to the consumer. The comment referred to its oral and written testimony submitted to FDA in connection with the September 29, 1982 hearing on the exclusivity policy.

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 21 CFR 330.1(c)(2), 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. All other OTC drug labeling required by a monograph or other regulation (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under the OTC drug monograph or other regulation where exact language has been established and identified by quotation marks, e.g., 21 CFR 201.63 or 330.1(g). The final rule in this document is subject to the labeling provisions in § 330.1(c)(2).

15. One comment requested the deletion of a portion of the directions proposed in § 358.150(d). The comment contended that directing patients to "Gently remove softened areas of the wart by rubbing with a wash cloth or emery board," and "Do not rub hard enough to cause bleeding," was not necessary and may not be in the best interest of the consumer. The comment explained that the consumer did not need to remove softened areas of the wart by rubbing and that the product would be effective without rubbing the wart as proposed in § 358.150(d). The comment contended that improper use of an emery board or washcloth could easily cause bleeding and subsequent infection.

This comment addressed directions proposed in the tentative final monograph published on September 3, 1982, and was received prior to publication of the reproposed tentative final monograph on March 27, 1987 (52 FR 9992). In that reproposal, the agency revised the directions proposed in § 358.150(d) and no longer included any directions about removing softened areas of the wart by rubbing. Thus, the comment's request was taken care of by the reproposed tentative final monograph.

16. One comment requested the deletion of the phrase in proposed § 358.150(d) that reads "preferably by encircling the wart with a ring of petrolatum." The comment contended that including only "petrolatum" in the warning may create the mistaken belief that petrolatum is the only acceptable protection. The comment added that such was not the Panel's finding, and many other types of protection could be used. Further, the comment argued that the word petrolatum may not be understood by consumers and, hence, may cause confusion. The comment concluded that the first part of the proposed directions statement, i.e., "Keep product away from surrounding skin" is sufficient to provide the consumer with directions to ensure correct usage of the product.

This comment addressed directions proposed in the tentative final monograph published on September 3, 1982, and was received prior to publication of the proposed tentative final monograph on March 27, 1987 (52 FR 9992). In that reproposal, the agency no longer included any directions about encircling the wart with a ring of petrolatum. In addition, the agency also did not include a direction to "keep the product away from surrounding skin." This decision was based on a discussion that appeared in the tentative final monograph for OTC corn and callus remover drug products, where the agency stated that 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. (See 52 FR 5412 at 5416.) Thus, the agency determined that the warning regarding avoiding contact with the surrounding skin is not necessary. Accordingly, the comment's request was taken care of by the reproposed tentative final monograph.

II. Summary of Significant Changes From the Proposed Rule

1. The agency has determined that a hydroscopic karaya gum pad with polypropylene backing meets the definition of a "plaster vehicle" in this final monograph. (See comment 5 above.) The agency is adding "salicylic acid 15 percent in a karaya gum, glycol plaster vehicle" to the list of active ingredients in § 358.110 and directions for this ingredient in § 358.150(d). (See comment 13 above.)

2. The agency has determined that a vehicle containing pyroxylin, volatile solvents, and a plasticizer meets the definition of a "collodion-like" vehicle in this final monograph. (See comment 7 above.)

3. The warnings proposed in § 358.150(c)(1) (ii) and (iii) are being combined, revised, and redesignated as § 358.150(c)(1)(ii). The warnings proposed in § 358.150(c)(1) (iv) and (v) are now redesignated as paragraphs (iii) and (iv). (See comment 11 above.)

4. The agency is revising the directions proposed in § 358.150(d) (1) and (2) to give manufacturers the option of including information about soaking the wart for 5 minutes in warm water prior to application of the wart remover drug product. (See comment 12 above.)

III. The Agency's Final Conclusions on OTC Wart Remover Drug Products

Based on the available evidence, the agency is issuing a final monograph establishing conditions under which OTC wart remover drug products are generally recognized as safe and effective and not misbranded. Specifically, the agency has determined that the only ingredients that meet monograph conditions are salicylic acid 12 to 40 percent in a plaster vehicle, salicylic acid 5 to 17 percent in a collodion-like vehicle, and salicylic acid 15 percent in a karaya gum, glycol plaster vehicle. All other ingredients for wart removal that were considered in this rulemaking are considered nonmonograph ingredients, i.e., acetic acid, glacial acetic acid, ascorbic acid, benzocaine, calcium pantothenate, camphor, castor oil, iodine, lactic acid, and menthol. Any drug product marketed for use as an OTC wart remover that is not in conformance with the monograph (21 CFR part 358, subpart B) is considered a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)) and misbranded under

section 502 of the act (21 U.S.C. 352) and can not be marketed for this use unless it is the subject of an approved application. An appropriate citizen petition to amend the monograph may also be submitted under 21 CFR 10.30.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (52 FR 9993). The agency has examined the economic consequences of this final rule in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this final rule for OTC wart 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 wart remover drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

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

List of Subjects in 21 CFR Part 358

Labeling, Over-the-counter drugs, Wart remover drug products.

Therefore, under the Federal Food, Drug, and Cosmetic Act, subchapter D of chapter I of title 21 of the Code of Federal Regulations is amended by adding new part 358 as follows:

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

Subpart A—[Reserved]

Subpart B—Wart Remover Drug Products

Sec.
358.101 Scope.
358.103 Definitions.
358.110 Wart remover active ingredients.
358.150 Labeling of wart remover drug products.

Authority: Sections 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

Subpart A—[Reserved]

Subpart B—Wart Remover Drug Products

§ 358.101 Scope.

(a) An over-the-counter wart 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 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.

§ 358.103 Definitions.

As used in this subpart:

(a) *Wart remover drug product.* A topical agent used for the removal of common or plantar warts.

(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.

§ 358.110 Wart remover active ingredients.

The product consists of any of the following active ingredients within the specified concentration and in the dosage form established for each ingredient.

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

(b) Salicylic acid 5 to 17 percent in a collodion-like vehicle.

(c) Salicylic acid 15 percent in a karaya gum, glycol plaster vehicle.

§ 358.150 Labeling of wart 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 "wart remover."

(b) *Indications.* The labeling of the product states, under the heading "Indications," any of the phrases listed in paragraph (b) of this section. Other truthful and nonmisleading statements, describing only the indications for use that have been established in paragraph (b) of this section, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (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 common warts. The common wart is easily recognized by the rough 'cauliflower-like' appearance of the surface."

(2) "For the removal of plantar warts on the bottom of the foot. The plantar wart is recognized by its location only on the bottom of the foot, its tenderness, and the interruption of the footprint pattern."

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

(1) *For products containing any ingredient identified in § 358.110.* (i) "For external use only."

(ii) "Do not use this product on irritated skin, on any area that is infected or reddened, if your are a diabetic, or if you have poor blood circulation."

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

(iv) "Do not use on moles, birthmarks, warts with hair growing from them, genital warts, or warts on the face or mucous membranes."

(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," consistent 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 § 358.110(a).* "Wash affected area." (Optional: "May soak wart in warm water for 5 minutes.") "Dry area thoroughly." (If appropriate: "Cut plaster to fit wart.") "Apply medicated plaster. Repeat procedure every 48 hours as needed (until wart is removed) for up to 12 weeks."

(2) *For products containing salicylic acid identified in § 358.110(b).* "Wash affected area." (Optional: "May soak wart in warm water for 5 minutes.") "Dry area thoroughly." Apply one drop at a time to sufficiently cover each wart. Let dry. Repeat this procedure once or twice daily as needed (until wart is removed) for up to 12 weeks."

(3) *For products containing salicyclic acid identified in § 358.110(c).* "Wash affected area." (Optional: "May soak wart in warm water for 5 minutes.") "Dry area thoroughly." (If appropriate: "Cut plaster to fit wart.") "Apply medicated plaster at bedtime, leave in place for at least 8 hours; in the morning, remove plaster and discard. Repeat procedure every 24 hours as needed (until wart is removed) for up to 12 weeks."

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

(f) The phrase "or podiatrist" may be used in addition to the word "doctor" in any of the labeling statements in this section when a product is labeled with the indication identified in § 358.150(b)(2).

Dated: June 27, 1990.

James S. Benson,

Acting Commissioner of Food and Drugs.

[FR Doc. 90-19029 Filed 8-13-90; 8:45 am]

BILLING CODE 4160-01-M