DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 358

[Docket No. 80N-0238]

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

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemeking.

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) wart 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 the advance notice of proposed rulemaking that was based on those recommendations. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs on the proposed regulation by November 2, 1982. New data by September 3, 1983. Comments on the new data by November 3, 1983. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Written comments on the agency's economic impact determination by January 3, 1983.

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

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

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, 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 could be submitted by February 2, 1981, in response to comments filed in the initial comment period.

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

The advance notice of proposed rulemaking, which was published in the **Federal Register** on October 3, 1980 (45 FR 65609), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the present document is designated in the OTC drug review regulations as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule) the FDA states for the first time its position on the establishment of a monograph for OTC wart 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 wart remover drug products.

No comments were received in response to the advance notice of proposed rulemaking. This proposal would amend Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations in Part 358 (as set forth elsewhere in this issue of the **Federal Register**) by adding Subpart B. This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC wart remover drug products as modified on the basis of the agency's independent evaluation of the Panel's report. Some modifications have been made for clarity and are reflected in this tentative final monograph.

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

In the advance notice of proposed rulemaking for OTC wart remover drug products (published in the **Federal Register** of October 3, 1980 (45 FR 65609)), the agency had suggested that the conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the **Federal Register** and that the conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of whether further testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

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

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss, but also interfere with consumers' access to safe and effective

drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the **Federal Register**. The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and have their products in compliance in the marketplace. However, if the agency determines that any labeling for a condition included in the final monograph should be implemented sooner, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmongraph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

FDA published in the **Federal Register** of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy,* 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision is now deleted from the regulations. The regulations now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process, before the establishment of a final monograph (46 FR 47738).

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

I. The Agency's Tentative Conclusions on the Comments

No comments were received by the agency on the advance notice of proposed rulemaking for OTC wart remover drug products.

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 concurs with the Panel's categorization of salicylic acid in concentrations of 5 to 17 percent in a collodion vehicle in Category I. The Panel placed benzocaine, camphor, castor oil, iodine (iodine sublimed), and menthol in Category II because it was not able to locate nor was it aware of data demonstrating the safety and effectiveness of these ingredients when used as OTC wart remover active ingredients. The agency also is not aware of any such data and, therefore, concurs with the Panel's classification of these ingredients.

The Panel placed glacial acetic acid, ascorbic acid, calcium pantothenate, and lactic acid in Category III because available data were insufficient to permit final classification. The Panel concluded that glacial acetic acid is safe in concentrations up to 11 percent, but there are insufficient data available to determine its effectiveness as a wart remover active ingredient. Although ascorbic acid, calcium pantothenate, and lactic acid were considered safe, there were insufficient data available to establish their effectiveness as wart remover active ingredients. FDA concurs with the Panel's classification of these ingredients.

The Panel placed the following combinations in Category III: (1) Salicylic acid (5 to 17 percent) with lactic acid (5 to 17 percent) in a collodion vehicle; (2) salicylic acid (5 to 17 percent with glacial acetic acid (11 percent) in a collodion vehicle; and (3) ascorbic acid (0.16 percent) with calcium pantothenate (0.20 percent).

The Panel concluded that lactic acid does not contribute to the effectiveness of combinations of salicylic and lactic acids and that salicylic acid is the active ingredient. The Panel also concluded that data are needed to demonstrate that lactic acid contributes to the increased effectiveness of the combination over that of salicylic acid alone in order to establish Category I status. Likewise, the Panel concluded that there is insufficient evidence to show that the addition of glacial acetic acid to salicylic acid increases the effectiveness of combinations of these ingredients. Therefore, data are needed to demonstrate that glacial acetic acid contributes to the increased effectiveness of the combination over that of salicylic acid alone in order to establish Category I status. The Panel also concluded that data are needed to demonstrate the contribution of the individual active ingredients for combinations of ascorbic acid (0.16 percent) and calcium pantothenate (0.20 percent) in order to establish Category I status.

FDA concurs with the Panel's classification of these combinations in Category III and agrees with the need for data to demonstrate individual ingredient contribution to the effectiveness of the combinations in order to establish Category I status.

For the convenience of the reader, the following table is included as a summary of the categorization of wart remover active ingredients:

Wart remover active ingredients	Panel	Agency
Acetic acid	III	III.
Acetic acid, glacial	III	III.
Ascorbic Acid	III	III.
Benzocaine	II	II.
Calcium pantothenate	III	III.
Camphor	II	II.
Castor oil	II	II.
Iodine (iodine, sublimed)	II	II.
Lactic acid	III	III.
Menthol	II	II.
Salicylic acid	I	I.

2. *Testing of Category II and Category III conditions.* The Panel recommended testing guideline for wart remover drug products (45 FR 65616). The agency is offering these guidelines as the Panel's recommendations without adopting them or making any formal comment on them. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety of effectiveness of any wart 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). This policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the agency's changes in the Panel's Recommendations

FDA has considered all relevant information and concludes that it will tentatively adopt the Panel's report and recommended monograph with the changes described in the summary below.

(1) In its recommended labeling for OTC wart remover drug products, the Panel included statements pertaining to limitation of use under both "Warnings," in § 358.150(c)(1)(iii), and *"Directions,"* in § 358.150(d). The warning statement reads, "If wart shows no improvement after 12 weeks of treatment, see your doctor." The directions for use read in part, "* * * Continue treatment until wart disappears, not to exceed 12

weeks." the agency believes that it is more useful to the consumer for both statments relating to limitation of use to appear in one place on the label. Because of the nature of the information conveyed, the agency believes it is more appropriate to include these statements under *"Directions."* Therefore, the agency proposes that the statement formerly included in the monograph as § 358.150(c)(1)(iii) be deleted and § 358.150(d) be expanded as follows: "* * * continue treatment until wart disappears, not to exceed 12 weeks. If no improvement is seen after 12 weeks, see a doctor."

(2) The agency has also made some changes in monograph format to conform to other OTC drug monographs and has combined several of the Panel's recommended label warnings, and made some changes in the wording of these warnings for clarity.

The agency has examined the economic consequences of this proposed rulemaking and has determined that it does not require either a Regulatory Impact Analysis, as specified in Executive Order 12291, or a Regulatory Flexibility Analysis, as defined in the Regulatory Flexibility Act (Pub. L. 96-354). Specifically, it would leave in Category I the main ingredient used in OTC wart remover drug products. Some reformulation and minor relabeling would be necesary, but resulting costs would be minimal. Therefore, the agency concludes that the proposed rule is not a major rule as defined in Executive Order 12291. Further, the agency certifies that the proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities, as defined in the Regulatory Flexibility Act.

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

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

List of Subjects in 21 CFR Part 358

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

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–4042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 as revised (see 47 FR 16010; April 14, 1982), it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended in Part 358 (as set forth elsewhere in this issue of the **Federal Register**) by adding new Subpart B, to read as follows:

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

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Subpart B—Wart Remover Drug Products

Sec
358.101 Scope
358.103 Definition.
358.110 Wart remover active ingredient.
358.150 Labeling of wart remover drug products.

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

Subpart B—Wart Remover Drug Products

§ 358.101 Scope.

(a) An over-the-counter wart remover drug product in a form suitable for topical administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this subpart in addition to each of the general conditions established in § 330.1.

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

§ 358.103 Definition.

As used in this subpart:

Wart remover drug product. A drug product applied to common or plantar warts to aid in their removal.

§ 358.110 Wart remover active ingredient.

The active ingredient and its concentration in the product is as follows: Salicylic acid 5 to 17 percent in a collodion 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 contains a statement of the indications under the heading "Indications" that is limited to one or both of the following phrases:

(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) "Do not use if you are a diabetic or have poor blood circulation because serious complications may result."

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

(3) "Discontinue use if excessive irritation occurs."

(4) "Do not use near eyes. If product accidentally comes in contact with eyes, flush eyes with water to remove film and continue to flush with water 15 minutes."

(5) "Highly flammable, keep away from heat, fire, or flame and store at room temperature."

(6) "Keep bottle tightly capped. Do not inhale."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions," followed by "or as directed by a doctor":

"Wash affected area and soak wart for 5 minutes. Gently remove softened areas of the wart by rubbing with a wash cloth or emery board. Do not rub hard enough to cause bleeding. Apply product once daily to the wart only. Keep product away from

surrounding skin preferably by encircling the wart with a ring of petrolatum. Continue treatment until wart disappears, not to exceed 12 weeks. If no improvement is seen after 12 weeks, see a doctor."

Interested persons may, on or before November 2, 1982 submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before January 3, 1983. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register.**

Interested persons, on or before September 3, 1982, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before November 3, 1983. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA–305) (address above). Received data and comments may also be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on November 3, 1983. Data submitted after the closing of the 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.

Dated: July 29, 1982.

Mark Novitch,

Acting Commissioner of Food and Drugs.

Richard S. Schweiker,

Secretary of Health and Human Services.

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