(B) *Depth.* The "Wattenberg J Sand" formation ranges from a depth of 7,600' to 8,400'. The average depth is approximately 8,000'.

(2) A more detailed description of the geographical extent and geological parameters of the designated tight formations is located in the Commission's official file for Docket No. RM79–76, and is also located in the official files of the jurisdictional agency which submitted the recommendation.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 357

[Docket No. 79N-0378]

Anthelmintic Drug Products for Over-the-Counter Human Use; Establishment of a Monograph

Correction

In FR Doc. 80–27587 appearing on page 59540 in the issue of Tuesday, September 9, 1980, make the following corrections:

(1) On page 59548, the word "not" should be inserted in the first line of paragraph (c)(1)(iii) of § 357.150 so that the paragraph reads as follows:

"(iii) 'Do not give to infants under 2 years of age or children who weigh less than 25 pounds, without first consulting a physician.' "

(2) In the first line of paragraph (c)(2) of the same section, ". . . gentain . . ." should have read ". . . gentian . . .".

BILLING CODE 1505-01-M

21 CFR Part 358

[Docket No. 80N-0238]

Wart Remover Drug Products for Over-the-Counter Human use; Establishment of a Monograph

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

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

DATES: Comments by January 2, 1981, and reply comments by February 2, 1981.

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

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD–510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–4860.

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on December 10, 1979 a report on wart remover drug products from the Advisory Review Panel on OTC Miscellaneous External Drug Products.

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

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

In accordance with § 330.10(a)92), the Panel and FDA have held as confidential all information concerning OTC wart remover drug products submitted for consideration by the Panel. All the submitted information will be put on public display in the Hearing Clerk's Office, Food and Drug Administration, after November 3, 1980, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD–510) (address above).

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

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

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

FDA published in the **Federal Register,** of May 13, 1980 (45 FR 31422) its proposal to revise the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy,* 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug regulations (21 CFR 330.10) are unlawful to the extent that they authorize the marketing of Category III drugs after a final monograph. Accordingly, the proposed regulations delete this provision and provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process, before the establishment of a final monograph (45 FR 31422).

Although it was not required to do so under *Cutler,* FDA has also decided to stop using the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III).

Any OTC drug product containing a "nonmonograph condition" will be subject to regulatory action after the establishment of a final monograph. This document, however, retains the concepts of Categories I, II, and III because that was the framework in which the Panel conducted its evaluation of the data.

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

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

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

Representatives of consumer and industry interests served as nonvoting members of the Panel. Marvin M. Lipman, M.D., of Consumers Union served as the consumer liaison. Gavin Hildick-Smith, M.D., served as industry liaison from January until August 1975, followed by Bruce Semple, M.D., until February 1978. Both were nominated by thr Proprietary Association. Saul A. Bell, Pharm. D., nominated by the Cosmetic, Toiletry, and Fragrance Association, also served as an industry liaison since June 1975.

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

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

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

The Panel was first convened on January 13, 1975 in an organizational meeting. Working meetings which dealt with the topic in this document were held on: August 5 and 6, September 30, October 1, December 11 and 12, 1977; April 16 and 17, June 11 and 12, August 11 and 12, September 17 and 18, 1978; January 14 and 15, March 11 and 12, May 18 and 19, August 3 and 4, September 28 and 29, October 29 and 30, and December 9 and 10, 1979.

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

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

Robert G. Blank, Ph. D.
Phillip R. Brachman, D.P.M.
Barry M. Brooks, J.D.
Frank E. Dunlap, M.D.
Donald E. Hartung
Adam Kara, D.P.M.
Robert Scheuplein, Ph. D.

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

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from interested persons, and has considered all pertinent information submitted through December 10, 1979 in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations set forth § 330.10, the Panel reviewed OTC wart remover drug products with respect to the following three categories:

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

Category II. Conditions under which OTC wart remover drug products are not generally recognized as safe and effective or are misbranded.

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

I. Submission of Data and Information

In an attempt to make this review as extensive as possible and to aid manufacturers and other interested persons, the agency compiled a list of ingredients recognized, either through historical use or use in marketed products, as wart remover active ingredients. Eleven ingredients were identified as follows: acetic acid, alcohol, benzocaine, camphor, castor oil, collodion, ether, glacial acetic acid, iodine sublimed, menthol, and salicylic acid. Notices were published in the **Federal Register** of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179) requesting the submission of data and information on these ingredients or any other ingredients used in OTC wart remover drug products.

A. Submissions

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

Firms and Marketed Products.

Commerce Drug Co., Inc., Farmingdale, NY 11735.—B/D/B/ Wart Remover.
Daywell Laboratories Corp., Fairfield, CT 06430.—Vergo.
Stiefel Laboratories, Inc., Oakhill, NY 12460—Duofilm, Duofilm-C.
Whitehall Laboratories, Inc., New York, NY 10017.—Compound-W.

B. Ingredients Reviewed by the Panel

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

Acetone
Alcohol
Ascorbic acid
Calcium pantothenate
Camphor
Castor oil
Ether
Flexible collodion
Glacial acetic acid
Lactic acid
Menthol
Salicylic acid
Starch

2. *Other ingredients reviewed by the Panel.*

Acetic acid
Benzocaine
Collodion
Iodine (iodine, sublimed)

C. Classification of Ingredients

1. *Active ingredients.*

Acetic acid
Acetic acid, glacial

Ascorbic acid
Benzocaine
Calcium pantothenate
Camphor
Castor oil
Iodine (iodine, sublimed)
Lactic acid
Salicylic acid

2. *Inactive ingredients.*

Acetone
Alcohol
Collodion
Ether
Flexible collodion
Starch

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

Benzocaine
Camphor
Castor oil
Iodine (iodine, sublimed)
Menthol

D. Referenced OTC Volumes

The "OTC Volumes" cited throughout this document include submissions made by interested persons in response to the call-for-data notices published in the **Federal Register** of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179). All the information included in these volumes, except for those deletions which are made in accordance with confidentiality provisions as set forth in § 330.10(a)(2), will be put on public display after November 3, 1980, in the Hearing Clerk's Office (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

II. General Discussion

All warts are caused by specific deoxyribonucleic acid (DNA) viruses of the papova group. These viruses infect the nucleus of epidermal cells and may be treated by destroying epeidermal cell together with the virus it contains (Ref. 1). There are several different virus types within this group (Ref. 2). Many tales are told about the cure of warts through the use of folk remedies, rituals, and placebos. One controlled study demonstrated that warts responded to hypnotic suggestion (Ref. 3). How the mind affects the virus is unknown, but the ability of many "wart cures" to cure warts must be ascribed either to the power of suggestion or to the spontaneous disappearance of the warts.

A patient may have one or hundreds of warts, which vary in appearance. The common wart, *Verruca vulgaris,* is a hard, grayish, sharply mariginated papule (solid elevation of the skin) with a rough, cauliflower-like surface. the filiform wart, *Verruca filiformis,* is a thread-like growth, while the digitate wart, *Verruca digitata,* is a cluster of filiform warts. The juvenile wart, *Veruca plana,* is a flat, tan-colored papule which occurs mainly on the face and back of hands of adolescents.

The plantar wart (and mosaic wart), *Verruca pantaris,* occurs only on the bottom of the foot. The Plantar wart is commonly tender because of its location on a weight-bearing area. Its surface is flat and may be hard and callused or soft and spongy. The normal plantar skin ridges encircle but do not cross it (as opposed to calluses). The mosaic wart is an irregularly shaped lesion with a granular surface formed by aggregation of nearby plantar warts. The genital wart, *Condyloma acuminata,* may resemble either a junvenile wart, a common wart, or even grow into a large mass having the appearance of a cauliflower-like surface. The genital wart is soft and occurs on the surface of the perineum. It also occurs in the vagina and anus.

All warts are histologically benign papillomas (noncancerous elevations) of the epidermis, and they never invade deeper tissues. If there is the slightest doubt about the clinical diagnosis, the wart must be examined histologically. Wart remover drug products should not be used on moles, birthmarks, or unusual warts with hair growing from them because premalignant and malignant lesions may be mistaken as warts. Use of these products will aggravate these conditions.

Several viruses of the papova group have been identified, but the number of these wart viruses is increasing (Ref. 2). Wart viruses look alike under the electron microscope, but can be distinguished by sophisticated biochemical and immunological tests. The viral etiology of warts was demonstrated 60 years ago by Wile and Kingery (Ref. 4). They excised warts, ground them, filtered the suspension through Berkefeld filters, and inoculated the filtrate into their own skin. Warts grew at the sites inoculated. Wile and Kingery's experiment was developed further by Mendelson and Kligman (Ref. 5) who grew material from plantar warts in monkey kindney tissue culture, and then inoculated the cell-free culture fluid into human volunteers; common warts resulted.

The experiments demonstrated the contagiousness of warts. The incubation period of experimental and naturally acquired warts can be as long as a year.

Warts frequently disappear spontaneously. In a 2-year study of children with warts, Massing and Epstein (Ref. 6) found that two-thirds of the warts initially seen disappeared completely without treatment. However, one-third of the patients developed new warts while their old ones were disappearing; the new warts developed three times as often in infected children as in uninfected children. Because of this tendency for auto-inoculation of the virus, i.e., producing warts in other sites, treatment of a wart is preferable to waiting for spontaneous disappearance. 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.

The Panel recommends that OTC wart remover drug products be used for the treatment of common and plantar warts only. The Panel concludes that because of the difficulty in recognizing and treating other types of warts they should not be subjected to self diagnosis and treatment except under the supervision of a doctor.

References

(1) Moschella, S. L., D. M. Pillsbury, and H. J. Hurley, "Dermatology," Volume I, W. B. Saunders Co., Philadelphia, pp. 574–582, 1975.

(2) Pass, F., "Progress Toward a New Wart Biology," *The Journal of Investigative Dermatology,* 70:109, 1979.

(3) Sinclair-Geiben, A. H. C., and D. Chalmers, "Evaluation of Treatment of Warts by Hypnosis," *The Lancet,* 2:480–482, 1959.

(4) Wile, U. J., and L. B. Kingery, "The Etiology of Common Warts," *Journal of the American Medical Association,* 73:970–973, 1919.

(5) Mendelson, C. G., and A. Kligman, "Isolation of Wart Virus in Tissue Culture," *Archives of Dermatology,* 83:559, 1961.

(6) Massing, A. M., and W. L. Epstein, "Natural History of Warts," *Archives of Dermatology,* 87:306–310, 1963.

III. Categorization of Data

A. Category I Conditions

These are conditions under which active ingredients used as wart removers are generally recognized as safe and effective and are not misbranded. The Panel recommends that the Category I conditions be effective 30 days after the date of

publication of the final monograph in the **Federal Register.**

1. Category I ingredient

Salicylic acid. The Panel concludes that salicylic acid is safe and effective for OTC use as a wart remover active ingredient in OTC topical drug products when used within the dosage limits specified in the dosage section stated below.

Salicylic acid, also known as 2-hydroxybenzoic acid and *o*-hydroxybenzoic acid, is found in nature in wintergreen leaves and in the bark of the sweet birch. It is synthesized by heating sodium phenolate with carbon dioxide under pressure. Salicylic acid is a lipid-soluble drug. One gram (g) dissolves in approximately 460 milliliters (mL) water or 15 mL boiling water, 2.7 mL alcohol, 3 mL acetone, 42 mL chloroform, 3 mL ether, 135 mL benzene, 52 mL oil turpentine, about 60 mL glycerol, or about 80 mL of fats or oils, which makes salicylic acid compatible with a variety of pharmaceutical vehicles (Ref. 1). The melting point is between 157° and 159° C.

The mechanical removal of epidermal cells infected with wart viruses is dependent on the keratolytic (peeling) effect of salicylic acid. The induction of a mild inflammatory reaction promotes the disappearance of a wart possibly by the immune mechanisms (Ref. 2).

a. *Safety.* Salicylic acid and its derivatives are a widely used group of compounds. They are used as analgesics (relieving pain), antipyretics (relieving fever), fungistatics (inhibiting fungi growth), keratolytics (peeling), rubefacients (reddening the skin), and have anti-inflammatory effects. Systemic absorption occurs whether the solicylates are administered orally, rectally, intravenously, or cutaneously. Whatever the mode of administration, the potential side effects of a doxic dose are essentially the same, i.e., nausea, decreased ability to hear, tinnitus (ringing in the ears), confusion, metabolic disturbances, hallucinations, and, in some extreme cases, death. These possible toxic reactions are collectively known as salicylism. The Panel is unaware of any report of salicylism occurring from the cutaneous use of salicylic acid as a wart remover.

Long-term use of salicylic acid in concentrations as low as 1 percent in petrolatum may cause damage on normal skin (Ref. 3). Salicylic acid softens and destroys the stratum corneum (outer layer of skin) by increasing endogenous hydration (water concentration), probably as a result of lowering the pH which causes the cornified epithelium (horny skin) to swell, soften, and then desquamate (shed). Damage and necrosis (cell death) of the normal skin have been associated with overuse.

A primary dermal (skin) irritation study using a 14-percent salicylic acid concentration in acetone collodion was performed using the standard Draize Irritation Test on white rabbits. The solution (0.5 mL) was applied to intact skin and abraded skin of six shaved albino rabbits. The test areas were covered by occlusive patches. The rabbits were observed at 24 and 72 hours. A 14-percent salicylic acid concentration in acetone collodion was found to be minimally irritating with a primary irritation factor of 0.25 on a scale ranging from 0 (no irritation) to 5.0 (corrosive). a 14-percent concentration of salicylic acid in collodion yielded a primary irritation factor of 1.0 (slightly irritating) (Ref. 4).

Rate of removal of warts is not as important as the safety in their removal. The use of concentrations as low as 1 percent salicylic acid for a long period of treatment is safer than the use of higher concentrations greater than 17 percent for a short period of time. The Panel concludes that due to the extreme keratolytic effect of salicylic acid, use of a concentration of salicylic acid higher than 17 percent to treat common or planter warts should be under the supervision of a doctor.

b. *Effectiveness.* Textbooks cite the longstanding use of salicylic acid preparations in the treatment of warts (Refs. 5 through 10). 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.

Salicylic acid used in the treatment of warts is usually formulated in flexible collodion. This vehicle contains pyroxylin, volatile solvents (ether, acetone, or alcohol), and plasticizers (camphor and castor oil). Pyroxylin is a nitrocellulose derivative, which after evaporation of the volatile solvents remains on the skin as an insoluble water-repellent film that is less likely to spread beyond the area applied than an aqueous system (Ref. 11). Ether is highly flammable and therefore must be stored at controlled room temperature away from heat. Because exposure of ether to air causes rapid evaporation, the bottle should be tightly capped. Inhalation of ether vapors should be avoided due to undesirable hypnotic effects. Collodion vehicles are advantageous because they form an adherent, flexible, or rigid film which keeps the active ingredient at the site of action and prevents migration to surrounding tissue (Ref. 12). They also prevent moisture evaporation from the skin, thereby facilitating penetration of the active ingredient into the affected area resulting in sustained local action of the drug.

In a study by Strakosch (Ref. 3) on normal skin, the activity of salicyclic acid in several ointment base vehicles was compared. A direct relationship between the concentration of salicyclic acid and the time required to produce the same keratolytic action was observed. A salicyclic acid concentration of 1 percent produced keratolysis in 10 days, while a 3-percent concentration caused a keratolytic action equal to the 1-percent results in about 8 days. When the concentration was increased to 5 percent, keratolysis equal to the results obtained with both 1 and 3 percent occurred in 7 days. When the concentration was increased from 5 to 10 percent, the time to produce keratolysis was reduced to approximately 3 days. Test results indicated that increasing the concentration above 10 percent produced little difference in keratolytic effect. Both 10 and 15 percent concentrations gave very similar results. None of the studies, however, were done to correlate the concentration of salicyclic acid with its keratolytic activity on warts.

In a study by Bunney, Nolan, and Williams (Ref. 2) involving 95 patients, a wart paint consisting of 16.7 percent salicyclic acid and 16.7 percent lactic acid in flexible collodion gave a cure rate of 67 percent for common warts and 84 percent for plantar warts. The study noted that the paint was applied nightly by the patient at home, and results were assessed at the end of 12 weeks. Other wart paints tested in these trials that did not contain salicyclic acid were significantly less effective. The cure rates cited for the wart paint combination are comparable to those achieved under the supervision of a doctor with the use of liquid nitrogen which is considered by many dermatologists to be the treatment of choice in removing warts (Ref. 13).

A double-blind study by Arndt and Clark (Ref. 14) evaluated a combination of 16.7 percent salicyclic acid and 16.7 percent lactic acid in flexible collodion against a placebo over a 4-week study period, after application to multiple lesions on anatomically matched sites. There were 34 patients with multiple lesions included in the study, 25 with common warts, 5 with juvenile warts, 3

with plantar warts and 1 with a genital wart. The test subjects were instructed to apply the lotions supplied to each set of preidentified lesions every 24 hours. Results demonstrated that 21 of 34 (72 percent) patients experienced improvement, the warts finally disappearing in 14 of the 21 (66 percent) test subjects and diminishing in size in the other 7 persons. Of the remaining 13 of 34 test subjects, the lesions were not improved in 8 (28 percent), and the 5 other patients dropped out of the study (Ref. 14).

A 4-week double-blind controlled study involving 50 patients, 25 using a combination of 5 percent salicyclic acid and 5 percent lactic acid in flexible collodion and 25 using a placebo, showed that 74 percent of the study warts were cleared or improved when using the active compound. Twenty-nine percent of the study warts were cleared or improved when using the placebo (Ref. 15).

Based on the current literature and wide clinical usage, the Panel concludes that salicyclic acid in a collodion vehicle is safe and effective as a keratolytic agent for the treatment of warts at concentrations of 5 to 17 percent. The Panel further concludes that where it is apparent that treatment is effective and that the wart is diminishing in size, treatment should continue until the wart disappears, but in no case should treatment continue for more than 12 weeks without the supervision of a doctor.

c. *Dosage.* Topical dosage is a preparation of 5 to 17 percent in a collodion vehicle.

d. *Labeling.* The Panel Recommends Category I labeling for wart remover active ingredients. (See Part III. paragraph A.2. below—Category I labeling.)

References

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

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

(4) OTC Volume 160283.

(5) Popovich, N. G., "Foot Care Products," *in* "Handbook of Nonprescription Drugs," 5th Ed., American Pharmaceutical Association, Washington, p. 364, 1977.

(6) Lerner, M. R., and A. B. Lerner, "Dermatologic Medications," The Year Book Publishers, Inc., Chicago, p. 35, 1960.

(7) DiPalma, J. R., "Drill's Pharmacology in Medicine," 4th Ed., McGraw-Hill, New York, p. 401, 1971.

(8) Swinyard, E. A., "Surface-Acting Drugs," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by L. S. Goodman, and A. Gilman, Macmillan Publishing Co., Inc., New York, P. 953, 1975.

(9) Osol, A., and R. Pratt, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 1034–1035, 1973.

(10) "The United States Pharmacopeia," 19th Ed., United States Pharmacopeial Convention, Inc., Rockville, MD, p. 446, 1975.

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

(12) Ansel, H. C., "Introduction to Pharmaceutical Dosage Forms," Lea and Febiger, Philadelphia, pp. 327–328, 1976.

(13) Arndt, K. A., "Manual of Dermatologic Therapeutics, 2d Ed., Little, Brown, and Co., Boston, pp. 211–219, 1978.

(14) Arndt, K. A., and J. E. Clark, "Double-Blind Study of Salicylic and Lactic Acid Lotion in Treating Warts," *Dermatology Digest*, 16:28, 1977.

(15) OTC Volume 160359.

2. *Category I labeling.* The Panel recommends the following labeling for Category I wart remover drug products:

a. *Indications.* (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."

b. *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, unusual warts with hair growing from them, genital warts, or warts on the face or mucous membranes."

(3) "If wart shows no improvement after 12 weeks of treatment, see your doctor."

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

(5) "Do not use near eyes."

(6) *For products containing collodion as a vehicle.*

(i) "Highly flammable, keep away from fire or flame."

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

(iii) "Keep bottle tightly capped."

(iv) "Avoid inhaling vapors."

(v) "If spilled on eyes, flush with water to remove film and flush with water an additional 15 minutes."

c. *Directions.* "Wash affected area and soak wart for 5 minutes. Gently remove softened area of the wart by rubbing with a wash cloth or emergy board. Do not rub hard enough to cause bleeding. Apply product once daily to the wart only. Continue treatment until wart disappears, not to exceed 12 weeks."

For products containing salicylic acid. "Keep product away from surrounding skin preferably by encircling the wart with a ring of petrolatum."

B. Category II Conditions.

These are conditions under which active ingredients used as wart removers are not generally recognized as safe and effective or are misbranded. The Panel recommends that the Category II Conditions be eliminated from OTC wart remover drug products effective 6 months after the date of publication of the final monograph in the Federal Register.

1. *Category II ingredients.* These ingredients are discussed elsewhere. (See Part I. paragraph C. above—Classification of Ingredients.)

2. *Category II labeling.* the Panel has examined the submitted labeling claims for wart remover drug products and has classified the following claims as Category II:

a. Claims implying a "quick," "painless," or "effective" removal of warts. Because wart remover drug products irritate surface tissue and treatment may require more than 1 week of use, the process may not be quick and can be painful depending on the individual wart. Because some warts may resist treatment of wart remover drug products, the Panel concludes that all OTC wart remover drug products are not "effective" for all warts and therefore disapproves of the word "effective" since most consumers will interpret this word to mean "100 percent effective" which it may not be.

b. Claims for use as a "keratolytic agent for the removal of benign epithelial tumors such as common warts" is unlikely to be understood by the majority of consumers because the terminology is scientific and implies that this product can be used to treat all benign epithelial tumors, and that the consumer will recognize the difference between benign and malignant tumors. The Panel concluded that OTC wart remover products should be labeled for treating common and plantar warts only.

C. Category III Conditions

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

1. Category III ingredients

Acetic acid, glacial
Ascorbic acid

Calcium pantothenate
Lactic acid

a. *Acetic acid, glacial.* The Panel concludes 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.

Glacial acetic acid is also known as concentrated acetic acid, crystallizable acetic acid, ethanolic acid, and vinegar acid. It contains 99.5 to 100.5 percent acetic acid ($C_2H_4O_6$) by weight. This acid is termed "glacial" because of its glassy appearance when solid. The freezing point is 15.6° C, and its boiling point is 118° C. the specific gravity is about 1.05 at 25° C. it has a molecular weight of 60.05 (Ref. 1).

It is a clear, colorless liquid with a pungent, characteristic odor. When diluted with water, it has an acid taste and is weakly ionized. It is miscible in water, alcohol, acetone, ether, and glycerin. It is immiscible in carbon tetrachloride and chloroform (Refs. 2 and 3). Glacial acetic acid is produced synthetically from acetylene.

Medicinally, glacial acetic acid is categorized as a vesicant (causing blistering) and as a caustic (corrosive) (Refs. 2 and 4).

(1) *Safety.* Caustics are used as topical agents to destroy warts.

According to DiPalma (Ref. 5), "local irritants (for example, glacial acetic acid) are applied in concentrations which destroy [wart] tissue." Care must be taken to apply the irritant only to the wart tissue. Necrosis (cell death) of the wart proceeds with some surrounding inflammation, and in a few days the wart may be removed (Ref. 5).

If the acid spreads onto healthy tissue, the burn should be treated immediately by flooding with water, followed by the application of sodium bicarbonate or chalk in powder form or by sodium bicarbonate in saline packs (Ref. 3).

A manufacturer (Ref. 6) submitted safety data in which the standard Draize Irritation Test was used to test an 11 percent glacial acetic acid in acetone collodion solution. The solution was applied to intact skin and abraded skin of six shaved albino rabbits. The results showed that, when describing irritation on a scale of 0 to 5.0, glacial acetic acid in acetone collodion is within the slightly irritating scale with a primary irritation factor of 1.10.

(2) *Effectiveness.* As a wart remover, glacial acetic acid may be applied with a cotton applicator. When applied to the wart, glacial acetic acid produces a mild-to-severe inflammation, often associated with hemorrhage beneath the wart. The inflammation may occur within several hours after the application of the acid. Exfoliation of the dessicated tissue takes place in 7 to 10 days (Ref. 7). However, there are insufficient data available on the effectiveness of the topical use of glacial acetic acid as a wart remover active ingredient. The only data available concern the combination of salicylic acid and glacial acetic acid. (See Part III. paragraph E. below—Combination Policy.)

(3) *Evaluation.* The Panel concludes that glacial acetic acid in concentrations up to 11 percent is safe, but there are insufficient data at this time to establish its effectiveness as a wart remover active ingredient, and therefore has placed this ingredient in Category III. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC wart remover ingredients. (See Part III. paragraph D. below—Data Required for Evaluation.)

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, p. 7, 1976.

(2) Swinyard, E. A., and W. Lowenthal, "Pharmaceutical Necessities," *in* "Remington's Pharmaceutical Sciences," 15th Ed., Edited by A. Osol, et. al., Mack Publishing Co., Easton, PA, pp. 1256–1257, 1975.

(3) Todd, R. G., "Extra Pharmacopeia. Martindale," 25th Ed., The Pharmaceutical Press, London, p. 4, 1967.

(4) Swinyard, E. A., "Surface-Acting Drugs," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by L. S. Goodman, and A. Gilman, MacMillan Publishing Co., Inc., New York, p. 953, 1975.

(5) DiPalma, J. R., "Drill's Pharmacology in Medicine," 4th Ed., McGraw-Hill, New York, pp. 1036–37, 1971.

(6) OTC Volume 160283.

(7) Sulzberger, M. B., et al., "Common Tumors of the Skin," *in* "Dermatology. Diagnosis and Treatment," The Year Book Publishers, Inc., Chicago, pp. 392–393, 1961.

b. *Ascorbic acid.* The Panel concludes that ascorbic acid is safe, but there are insufficient data available to determine its effectiveness as a wart remover active ingredient.

Ascorbic acid, or vitamin C, has the molecular formula $C_6H_8O_6$ and a molecular weight of 176.13. It is stable when dry, but is easily oxidized in aqueous solution in the presence of air. Oxidation is accelerated by heat, light, alkalies, oxidative enzymes, and traces of copper and iron. In solution it has a pleasant, sharp, acidic taste and a pH of 2. One gram of ascorbic acid dissolves in about 3 mL water; it is insoluble in ether, chloroform, benzene, petroleum ether, oils, fats, and fat solvents (Refs. 1, 2, and 3).

Ascorbic acid is an essential coenzyme for collagen formation, tissue repair, and synthesis of lipids and proteins. It acts as a reducing agent, as an antioxidant, and is necessary for many physiological functions (e.g., metabolism of iron and folic acid, resistance to infection, preservation of blood vessel tonicity). Ascorbic acid is readily absorbed from the small intestine. After tissue saturation occurs, the excess is excreted by the kidneys (Ref. 4).

(1) *Safety.* Clinical toxicity is low. No harmful effects have been noted with single doses of 1 to 6 g in adults, even when given intravenously, or when plasma concentrations each 5 to 22 mg/100 mL, or with oral administration of 1 g daily (Ref. 5).

A daily intake of 20 to 20 mg ascorbic acid is sufficient to protect an adult from classical scurvy. Forty-five mg is the Recommended Dietary Allowance (RDA) for both males and females over 11 years of age.

The prolonged ingestion of supplements of ascorbic acid in excess of about 3 g daily is not with potential danger. Gastrointestinal disturbances (nausea followed by some diarrhea), kidney or bladder stone formation (resulting from an increased excretion of oxalate, urate, and calcium), prenatal conditioning of the fetus to deficiency symptoms, interferences with simple tests for glycosuria, and interference with the anticoagulant effect of heparin are clinical problems which may occur (Ref. 1).

(2) *Effectiveness.* There are insufficient data available on the effectiveness of the topical use of ascorbic acid as a wart remover active ingredient. The only data available concern the combination of ascorbic acid with calcium pantothenate. (See Part III. paragraph E. below—Combination Policy.)

(3) *Evaluation.* The Panel concludes that ascorbic acid is safe, but there are insufficient data available at this time to establish its effectiveness, and therefore has placed this ingredient in Category III. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC wart remover ingredients. (See Part III. paragraph D. below—Data Required for Evaluation.)

References

(1) Boehne, J. W., and M. R. Fox, "Vitamins and Other Nutrients," *in* "Remington's Pharmaceutical Sciences," 15th Ed., Edited by A. Osol, et. al., Mack Publishing Co., Easton, PA, pp. 946–948, 1975.

(2) "The United States Pharmacopeia," 19th Ed., United States Pharmacopeial

Convention, Inc., Rockville, MD, pp. 36–37, 1975.

(3) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, pp. 110–111, 1976.

(4) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, pp. 188–190, 1977.

(5) Sollman, T., "Nutritional Vitamins," *in* "A Manual of Pharmacology," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 89–94, 1957.

c. *Calcium pantothenate.* The Panel concludes that calcium pantothenate is safe, but there are insufficient data available to determine its effectiveness as a wart remover active ingredient.

Calcium pantothenate is the calcium salt of pantothenic acid. It has the molecular formula $C_{18}8H_{32}CaN_2O_{10}$ and a molecular weight of 476.53. It decomposes between 195° to 196° C, is moderately hygroscopic, and reasonably stable to air and light. One gram dissolves in 2.8 mL water. It is soluble in glycerin, but it is only slightly soluble in alcohol and acetone. The pH of an aqueous solution (1 in 20) is between 7.2 and 8.0. Solutions are most stable between pH 5 and 7 (Ref. 1).

Pantothenic acid (cyanocobalamine) is a component of coenzyme A which is necessary for various metabolic reactions within the body. Pantothenic acid is essential for the intermediary metabolism of carbohydrates, fats, and protein. No proven cases of spontaneously occurring clinical deficiency have been observed.

Pantothenic acid is present in almost all plant and animal tissue, and a balanced 2,500 calorie diet contains about 10 mg. A Recommended Daily Allowance (RDA) has not been established, but an intake of 5 to 10 mg is believed to be adequate (Refs. 2 and 3).

(1) *Safety.* Pantothenic acid is included in multiple vitamin prepartions as the calcium or sodium salt. It is essentially nontoxic (Ref. 3). It has been stated that 0.8 to 10g/kg body weight can cause death by respiratory failure. Prolonged feedings with subtoxic doses do not cause any symptoms (Ref. 4).

Experimentally, pantothenic acid deficiency has been produced by administering a metabolic antagonist, *omega*-methylpantothenic acid, together with a semisynthetic diet low in the vitamin. The deficiency is characterized by weakness, fatigue, headache, nausea, muscle cramps, and poor muscle coordination (Ref. 3).

The Panel believes that calcium pantothenate is safe as a topical agent because of its safe usage internally.

(2) *Effectiveness.* There are insufficient data available on the effectiveness of the topical use of calcium pantothenate as a wart remover active ingredient. The only data available are on the combination of calcium pantothenate and ascorbic acid. (See Part III. paragraph E. below—Combination Policy.)

(3) *Evaluation.* The Panel concludes that calcium pantothenate is safe, but thee are insufficient data available at this time to establish its effectiveness and therefore has placed this ingredient in Category III. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC wart remover ingredients. (See Part III. paragraph D. below—Data Required for Evaluation.)

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, p. 214, 1976.

(2) Greengard, P., "Water-Soluble Vitamins," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by L. S. Goodman, and A. Gilman, MacMillan Publishing Co., Inc., pp. 1558–1559, 1975.

(3) "AMA Drug Evaluation," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, pp. 191–192, 1977.

(4) Sollman, T., "Nutritional Vitamins," *in* "A Manual of Pharmacology," 8th Ed., W. B. Saunders Co., Philadelphia, p. 117, 1957.

d. *Lactic acid.* The Panel concludes that lactic acid is safe, but there are insufficient data available to determine the effectiveness of lactic acid as an OTC wart remover active ingredient when used within the dosage limits specified in the proposed dosage section stated below.

Lactic acid is a weak acid, syrupy in consistency, colorless or yellowish, and nearly odorless. Lactic acid absorbes water on exposure to moist air. When a solution is concentrated to above 50 percent by boiling, lactic acid lactate begins to form. Concentrated lactic acid is mixture of lactic acid ($C_3H_6O_3$) and lactic acid lactate ($C_6H_{10}O_5$). Lactic acid is also known as 2-hydroxypropanoic acid. It has the equivalent of 85 to 90 percent by weight of lactic acid with the anhydride, lactic acid lactate, amounting to 10 to 15 percent. Lactic acid has a specific gravity of about 1.20. It decomposes when distilled under normal pressure, but may be distilled without decomposition under reduced pressure. It is soluble in water, alcohol, and ether, and it is insoluble in chloroform. The melting point is 16.8° C, and the boiling point is 82° to 85° C (Ref. 1).

(1) *Safety.* The process of glycolysis in tissues consists of the breakdown of glycogen, glucose, or other sugars to pyruvic and lactic acids (Ref. 2). This is a process of carbohydrate metabolism generally characteristic of animal cells. Thus, lactic acid is normally present in all cells of the body in small amounts. Lactic acid accumulates in tissues only when oxidation cannot keep up with glycolytic reaction, and pyruvic acid is reduced to lactic acid (Ref. 3). Lactic acidosis, as well as an organ hypoperfusion (reduced blood volume in organs) may result in poor tissue oxygenation.

According to Driesbach (Ref. 4) lactic acid has a corrosive effect when used topically in high concentration.

Van Scott and Yu (Ref. 5) found that concentrations of lactic acid in topically applied products generally range from 5 to 10 percent. While 5 to 10 percent lactic acid has been used in most instances on test sites, it was found that a 2- to 5-percent lactic acid was better for treatment of ichthyosis (dryness, roughness, and scaliness) on large areas or on the whole body because it was less irritating.

Irritancy resulting from the usage of 10 percent concentration of lactic acid was readily reversed by temporary discontinuance or by reducing frequency of applications (Ref. 5).

(2) *Effectiveness.* Lactic acid has been used for many years in the treatment of warts and is still included in the formula of wart paints appearing in some pharmacopeias (Ref. 6). Van Scott and Yu (Ref. 5) have extensively evaluated the control of keratinization with α-hydroxy acids and support the use of lactic acid as a keratolytic. Twelve α-hydroxy acids plus 48 other materials were studied. Lactic acid, in a 5 percent concentration, gave the most improvement (return to normal skin) in patients with ichthyosiform dermatoses (a scaly skin disease). These were all severe congenital hyperkeratotic problems such as: lamellar ichthyosis (a skin disorder characterized by roughness, redness, or scaliness), x-linked ichthyosis, ichthyosis vulgartis, epidermolytic hyperkeratosis, and undiagnosed types. Test sites, 3 to 6 centimeters (cm) in diameter, were circumscribed on the skin; biopsies were performed; and clinical observations were made either daily or weekly. The substances tested were fatty acids, lower molecular weight organic mono- and di-acids, aromatic acids including salicylic acid and analogues thereof, amino acids, urea, and structurally related compounds. The α-hydroxy acids gave the most improvement while the other substances tested gave little or no improvement. It was noted that in most instances, although 5 to 10 percent concentrations were used on test sites, a 2 to 5 percent concentration was found to be better for use on larger areas due to a lower potential to cause irritation.

The degree of irritancy caused by 10 percent concentrations was mild and quickly detected by patients. Preparations used in the testing were water-in-oil and oil-in-water emulsion base ointments and creams. Except for personal patient preference, the type of vehicle used has not been a major factor to determine final effectiveness (Ref. 5). Many of the preparations tested were in hydrophilic ointment. Although none of the tests were done on warts, this reference is cited because of the similarity between the treatment of hyperkeratosis of ichthyosis and the treatment of hyperkeratosis of warts.

According to Van Scott and Yu (Ref. 5), lactic acid appears to influence the process of keratinization, but does not seem to be a keratolytic agent by itself.

Van Scott and Yu found that lactic acid is one of a group of compounds which modify keratinization in ichthyosis. Histologically (microscopically), 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 is a significant shedding to reduce the thickness of the epidermis.

In a study by Bunney, Nolan, and Williams (Ref. 6) lactic acid in combination with salicylic acid was cited as having been used for many years in the treatment of warts and is still included in the formula of wart paints appearing in some pharmacopeiae. A paint consisting of 1 part salicylic acid (16.7 percent), 1 part lactic acid (16.7 percent), and 4 parts collodion was used in this study. This preparation proved to be very effective (70 percent cure rate) in the treatment of common warts.

A double-blind controlled study (Ref. 7), involving 50 patients, comparing a combination of 5 percent salicylic acid and 5 percent lactic acid in flexible collodion with a placebo during a week study period, showed that 74 percent of the study warts were cleared or improved for 25 patients using the active compound, and that only 20 percent of the study warts were cleared or improved for 25 patients using the placebo.

The Panel could find no data on the use of lactic acid alone in treatment of warts. The only data available to the Panel concerning lactic acid in the treatment of warts was lactic acid in combination with salicylic acid. (See Part III, paragraph E. below—Combination Policy.)

(3) *Proposed dosage.* Topical dosage is 5 to 17 percent lactic acid in a collodion vehicle.

(4) *Labeling.* The Panel recommends the Category I labeling for wart remover active ingredients. (See Part III, paragraph A.2. above—Category I labeling.)

(5) *Evaluation.* The Panel concludes that lactic acid is safe, but there are insufficient data available at this time to establish its effectiveness, and, therefore, the Panel has placed this ingredient in Category III. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC wart remover ingredients. (See Part III, paragraph D. below—Data Required for Evaluation.)

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, pp. 700–701, 1976.

(2) West, E. S., et al., "Carbohydrate Metabolism," *in* "Textbook of Biochemistry," 4th Ed., Macmillan Publishing Co., Inc., New York, p. 1075, 1965.

(3) Levinsky, N. G., "Acidosis and Alkalosis," *in* "Harrison's Principles of Internal Medicine," 8th Ed., Edited by G. W. Thorn, et al., McGraw-Hill Book Co., New York, p. 379, 1977.

(4) Dreisbach, R. H., "Handbook of Poisoning: Diagnosis and Treatment," 9th Ed., Lange Medical Publications, Los Altos, CA, pp. 188–193, 1977.

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

(6) 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.

(7) OTC Volume 160359.

2. *Category III labeling.* The Panel was unable to identify any Category III labeling.

D. Data Required for Evaluation

The Panel considers the protocols recommended in this document for the studies required to bring a Category III ingredient into Category I to be in agreement with the present state of the art and does not intend to preclude the use of any advances or improved methodology in the future.

1. *Methods of study.* The Panel recognizes that there are few if any appropriate methods or protocols for determining the safety and effectiveness of wart remover active ingredients. Additionally, little is known regarding the growth pattern, immunology, or metabolism of the human papilloma (wart) virus. However, in recent years some success has been achieved in growing this virus in tissue culture (Refs. 1 and 2). The Panel encourages the further development of an invitro tissue culture method which may possibly be utilized in assaying drug effectiveness against the wart virus.

2. *Effectiveness.* It is necessary to determine the effectiveness of wart remover ingredients through human testing. A properly designed double-blind study should be performed in which the ingredient is shown to provide a significantly higher rate of wart removal as compared to the placebo. A 12-week testing period with observation every 7 to 14 days should be used for both common and plantar warts. A 95-percent probability level can be obtained by specifying that at least a 20-percent difference be found in a double-blind test between the control and treatment groups. This test would take into account the high rate of spontaneous remissions (estimated to be as high as 30 percent).

The following guidelines are given as examples:

The clinical trial must show at least a 20-percent difference in cure rate between the treatment and the control group; the high rate of spontaneous remissions necessitates the use of a very large patient population to show that the difference is not a chance one, i.e., a 20-percent difference requires 315 patients. A 1-percent difference requires 130,000 patients; persons with common or plantar warts may be used; the method of application should be demonstrated, and the study carried out by a doctor.

References

(1) Eisinger, M., et al., "Propagation of Human Wart Virus in Tissue Culture," *Nature*, 256:432–434, 1975.

(2) Lancaster, W. D., and W. Meinke, "Persistence of Viral DNA in Human Cell Cultures Infected with Human Papilloma Virus," *Nature*, 256:434–436, 1975.

E. Combination Policy

In reviewing OTC wart remover drug combinations the Panel applied the regulation in § 330.10(a)(4)(iv) which states:

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

therapy for a significant proportion of the target population.

The Panel concurs with this regulation.

In addition, the Panel believes that active ingredients from the same therapeutic category that have the same mechanism of action should not ordinarily be combined unless there is some advantage on a benefit-to-risk basis over the single ingredients in terms of enhanced effectiveness, safety, patient acceptance, or quality of formulation.

However, in some cases an ingredient may contribute to safety and effectiveness only when used in a specific combination. In such cases the ingredient will be permissable in the specific combinations and not as a single ingredient.

The Panel does not recommend any Category I or Category II combinations.

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

1. *Salicylic acid (5 to 17 percent) with lactic acid (5 to 17 percent) in a collodion vehicle.* In the study, by Bunney, Nolan, and Williams (Ref. 1), involving 95 patients, a wart paint consisting of 16.7 percent salicylic acid and 16.7 percent lactic acid in flexible collodion gave a cure rate of 67 percent for common warts and 84 percent for simple plantar warts. The study noted that the paint was applied nightly by the patient at home. The cure rates cited for the wart paint combination are comparable to those achieved under the supervision of a doctor with the use of liquid nitrogen, which is considered by many dermatologists to be the treatment of choice in removing warts.

A double-blind study by Arndt and Clark (Ref. 2) evaluated, during a 4-week period, a combination of 16.7 percent salicylic acid and 16.7 percent lactic acid in flexible collodion against a placebo, applied to multiple lesions on anatomically matched sites. Thirty-four patients with multiple lesions were studied. Of the 34 patients, 25 had common warts, 5 had juvenile warts, 3 had plantar warts, and 1 had a genital wart. The test subjects were instructed to apply the lotions supplied to each set of preidentified lesions every 24 hours. Results demonstrated that 21 of 34 patients (72 percent) experienced improvement, the warts disappearing in 14 of the 21 'improved' test subjects (66 percent) and diminishing in size in the other 7 subjects. Of the remaining 13 test subjects, the lesions were not improved in 8 (28 percent), and the 5 other patients dropped out of the study (Ref. 2).

A 4-week double-blind controlled study involving 50 patients, 25 using a combination of 5 percent salicylic acid and 5 percent lactic acid in flexible collodion and 25 using a placebo, showed that 74 percent of the study warts were cleared or improved when using the active compound. Twenty-nine percent of the placebo group warts were cleared or improved (Ref. 3).

The Panel has placed salicylic acid alone in Category I, but could find no data on the use of lactic acid alone in the treatment of warts. The Panel feels that the lactic acid does not contribute greatly to the effectiveness of the combination and that salciylic acid is the active ingredient which acts as a keratolytic agent reducing the pool of virus present in the keratin layer as well as lower in the epidermis and which stimulates an immune response by provoking a mild inflammatory reaction.

The Panel concludes that data which shows that lactic acid contributes to the increased effectiveness of the combination over that of salicylic acid alone is needed to established Category I conditions.

2. *Salicylic acid (5 to 17 percent) with glacial acetic acid (11 percent) in a collodion vehicle.* In an uncontrolled study (Ref. 4) on the effectiveness of a wart paint containing 14.2 percent salicylic acid and 11 percent glacial acetic acid in collodion on 36 patients, 27 had common warts, 6 had plantar warts, and 3 had soft corns. It was found that 13 of the patients with common warts were cured after 1 week, and 7 more were cured after 2 weeks. After 3 weeks, four warts were removed by cutting away. The remaining three warts were electro-desiccated (burned off). None of the patients with plantar warts was cured after 1 week. Two patients with plantar warts were cured after 2 weeks therapy and deep curettage. (Ref. 4). The Panel concludes that there is insufficient evidence to show that the addition of glacial acetic acid to salicylic acid increases its effectiveness as a wart remover.

3. *Ascorbic acid (0.16 percent) and calcium pantothenate (0.20 percent).* A preparation containing 0.16 percent ascorbic acid and 0.20 percent calcium pantothenate in a starch base has been used for the past 23 years to treat warts. According to the manufacturer (Ref. 5) it is painless and safe.

Linn (Ref. 6) treated 109 patients with this preparation of 0.16 percent ascorbic acid and 0.20 percent calcium pantothenate twice daily for 2 or more weeks (some for over 6 weeks). Seventy-one of this study group had common warts and 38 had plantar warts. Of those with common warts, 27 percent were cured and 46 percent were improved. Of those with plantar warts, 29 percent were cured and 29 percent were improved. A strikingly higher rate of response was seen at 2 weeks and at 4 weeks than at later periods. Warts which had been present for less than 6 months were more likely to respond than warts of longer duration. Linn's study was not controlled, and her results along with others such as Brezaks (Ref. 7) can be ascribed to suggestion or to the spontaneous disappearance of warts.

One controlled study was performed by Reiss (Ref. 7) on 10 patients with multiple-bilateral warts. On the right side of the body, the ascorbic acid-calcium pantothenate paste was applied; on the left side of the body, a "control" ointment was applied. Six patients with bilateral (on both sides) warts on hands and arms gave the following results: 3 were cured on the right side but not on the left; 2 improved faster on the right side than on the left; 1 was refractory (no improvement) bilaterally. Four patients with plantar warts showed the following results: none of the lesions treated with the control showed improvement; two patients, one with two lesions and one with three lesions showed a complete cure in 5 and 6 weeks respectively when treated with the active medication. Two other patients showed no response after 8 weeks of treatment with the active medication. Reiss concluded that the medication was effective, but "biostatistical data compiled from a larger number of patients would be more desirable for a final evaluation."

The Panel concludes that data showing contribution of the individual active ingredients to the effectiveness of the combination is needed to establish Category I conditions.

References

(1) 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.

(2) Arndt, K. A., and J. E. Clark, "Double-Blind Study of Salicylic and Lactic Acid Lotion in Treating Warts," *Dermatology Digest*, 16:28, 1977.

(3) OTC Volume 160359.

(4) OTC Volume 160004.

(5) OTC Volume 160287.

(6) Linn, E., "Conservative Management of Warts," *Clinical Medicine*, 74:39–42, 1967.

(7) Letter solicited by Daywell Laboratories Corporation in OTC Volume 160287.

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

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)) and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)) and under authority delegated to the Commissioner (21 CFR 5.1), it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended by adding to Part 358, new Subpart B, to read as follows:

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

* * * * *

Subpart B—Wart Remover Drug Products

Sec.

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

Subpart 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 condition in this subpart and each general condition established in § 330.1 of this chapter.

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

§ 358.103 Definitions.

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

§ 358.110 Wart remover active ingredient.

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) *For products containing any ingredient identified in § 358.110.* (i) "Do not use if you are a diabetic or have poor blood circulation because serious complications may result."

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

(iii) "If wart shows no improvement after 12 weeks of treatment, see your doctor."

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

(v) "Do not use near eyes."

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

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

(iii) "Keep bottle tightly capped."

(iv) "Avoid inhaling vapors."

(v) "If spilled on eyes, flush with water to remove film and flush with water an additional 15 minutes."

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

(1) *For products containing any ingredient identified in § 358.110.* "Wash affected area and soak wart for 5 minutes. Gently remove softened area 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. Continue treatment until wart disappears, not to exceed 12 weeks."

(2) *For products containing salicylic acid identified in § 358.110.* "Keep product away from surrounding skin preferably by encircling the wart with a ring of petrolatum."

Interested persons are invited to submit their comments in writing (preferably in four copies and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal on or before January 2, 1981. Comments should be addressed to the Hearing Clerk (HFA–305), Food and Drug Administration, Rm 4–62, 5600 Fishers Lane, Rockville, MD 20857, and may be accompanied by a supporting memorandum or brief. Comments replying to comments may also be submitted on or before February 2, 1981. Comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

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

Dated: September 25, 1980.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

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21 CFR Part 444

[Docket No. 79 N–0341; DESI Nos. 8615, 9152, 9188, and 50188]

Oligosaccharide, Peptide, and Certain Other Antibiotic Drugs

Correction

In FR Doc. 80–26520 appearing on page 57735 in the issue of Friday, August 29, 1980, make the following correction:

(1) On page 57736, third column, the word "drug" was misspelled in the following three places: the fourteenth line of the second complete paragraph, the third line of the third complete paragraph, and the seventh line of the fourth complete paragraph.

(2) On page 57737, column one, the bold face heading for § 444.342a should have appeared as follows: