DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 347

[Docket No. 78N-0021]

Skin Protectant Drug Products for Over-the-Counter Human Use; Establishment of a Monograph; and Reopening of Administrative Record

AGENCY: Food and Drug Administration.

ACTION: Advance notice of proposed rulemaking and reopening of administrative record.

SUMMARY: The Food and Drug Administration (FDA) is issuing an advance notice of proposed rulemaking that would establish conditions under which over-the-counter (OTC) skin protectant drug products used (1) for the treatment of diaper rash; (2) for the prevention of poison ivy, oak, and sumac; (3) for the treatment of fever blisters; (4) as astringents; and (5) as insect bite neutralizers are generally recognized as safe and effective and not misbranded. This notice relates to the development of a monograph for skin protectant drug products in general, which is part of the ongoing review of OTC drug products conducted by FDA. This notice also reopens the administrative record for OTC skin protectant drug products to allow for consideration of recommendations on external analgesic drug products for the five drug categories listed above that have been received from the Advisory Review Panel on OTC Miscellaneous External Drug Products.

DATES: Written comments by December 6, 1982 and reply comments by January 5, 1983.

ADDRESS: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

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

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on December 14 and 15, 1980 statements from the Advisory Review Panel on OTC Miscellaneous External Drug Products relating to OTC drug products intended for use (1) in the treatment of diaper rash; (2) for the prevention of poison ivy, oak, and sumac; (3) for the treatment of fever blisters; (4) as astringents; and (5) as insect bite neutralizers. FDA regulations (21 CFR 330.10(a)(6)) provide that the agency issue in the **Federal Register** a proposed rule containing (1) the monograph recommended by the Panel, which establishes conditions under which these OTC drug products are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs' not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

Because some ingredients in the five drug categories listed above are marketed in OTC drug products as skin protectants, FDA has determined that the Miscellaneous External Panel's recommendations on OTC drug products for these uses should be included as part of the proposed rulemaking for skin protectant drug products. Development of this rulemaking has been ongoing for some time.

In the **Federal Register** of August 4, 1978 (43 FR 34628), FDA issued an advance notice of proposed rulemaking to establish a monograph for OTC skin protectant drug products. FDA advises that it is reopening the administrative record for OTC skin protectant drug products only as it pertains to drug products for the five drug categories listed above in order to allow for the consideration of the Miscellaneous External Panel's recommndations on these products. Comments received on this advance notice of proposed rulemaking will be addressed in a future issue of the **Federal Register**. Also, the proceedings to develop monographs for drug products for the treatment of diaper rash; for the prevention of poison ivy, oak, and sumac; for the treatment of fever blisters; for astringents; and for insect bite neutralizers will be merged with the general proceeding to establish a monograph for OTC skin protectant drug products.

The Panel did not recommend any Category I conditions for skin protectant ingredients contained in drug products for the treatment of diaper rash; for the prevention of poison ivy, oak, and sumac; for the treatment of fever blisters; and as insect bite neutralizers. Therefore, no new sections to Part 347 (as set forth in the advance notice of proposed rulemaking for skin protectant drug products that was published in the **Federal Register** of August 4, 1978 (43 FR 34628)) are included in this advance notice of proposed rulemaking for these drug categories. The Panel did recommend Category I conditions for astringent drug products. Therefore, for this drug category, amendments to Part 347 are included in this advance notice of proposed rulemaking (§§ 347.3(a), 347.12, and 347.52).

The unaltered statements of the Panel relating to OTC skin protectant ingredients contained in drug products for the treatment of diaper rash; for the prevention of poison ivy, oak, and sumac; for the treatment of fever blisters; as astringents; and as insect bite neutralizers is issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The statements have been prepared independently of FDA, and the agency has not yet fully evaluated the Panel's recommendations. The Panel's findings appear in this document to obtain public comment before the agency reaches any decision on the Panel's statements. This document represents the best scientific judgment of the Panel members, but does not necessarily reflect the agency's position on any particular matter contained in it.

After reviewing all comments submitted in response to this document, FDA will issue in the **Federal Register** a tentative final monograph for OTC skin protectant drug products, to include the five drug categories listed above. Under the OTC drug review procedures, the agency's position and proposal are first stated in the tentative final monograph, which has the status of a proposed rule. Final agency action occurs in the final monograph, which has the status of a final rule.

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

Register of December 11, 1979; 44 FR 71742).

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC skin protectant drug products used for the treatment of diaper rash; for the prevention of poison ivy, oak, and sumac; for the treatment of fever blisters; as astringents; and as insect bite neutralizers. 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 skin protectant drug products relating to the five drug categories listed above should be accompanied by appropriate documentation. Comments will not be accepted at this time on any portion of the OTC skin protectant rulemaking other than that relating to drug products for the five listed drug categories.

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information concerning OTC drug products for the treatment of diaper rash; for the prevention of poison ivy, oak, and sumac; for the treatment of fever blisters; as astringents; and as insect bite neutralizers submitted for consideration by the Panel. All the submitted information will be put on public display in the Dockets Management Branch, Food and Drug Administration, after October 7, 1982, except to the extent that the person submitting it demonstrates that it falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureaus of Drugs and Biologics (HFD-510) address above).

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

Although it was not required to do so under *Cutler*, FDA will no longer use the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III because that was the framework in which the Panel conducted its evaluation of the data.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the **Federal Register.** In some advance notices of proposed rulemaking previously published in the OTC drug review, the agency suggested an earlier effective date. However as explained in the tentative final monograph for OTC topical antimicrobial drug products (published in the **Federal Register** of July 9, 1982; 47 FR 29986), the agency has concluded that, generally, it is more reasonable to have a final monograph be effective 12 months after the date of its publication in the **Federal Register.** This period of time should enable manufacturers to reformulate, relabel, or take other steps to comply with a new monograph with a minimum disruption of the marketplace thereby reducing economic loss and ensuring that consumers have continued access to safe and effective drug products.

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

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was announced in the **Federal Register** of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the **Federal Register** of May 11, 1972 (37 FR 9464). In accordance with these regulations, a request for data and information on all active ingredients used in OTC miscellaneous external drug products was issued in the **Federal Register** of November 16, 1973 (38 FR 31697). (In making their categorizations with respect to "active" and "inactive" ingredients, the advisory review panels relied on their expertise and understanding of these terms. FDA has defined "active ingredient" in its current good manufacturing practice regulations (§ 210.3(b)(7), (21 CFR 210.3(b)(7))), as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." An "inactive ingredient" is defined in § 210.3(b)(8) as "any component other than an "active ingredient.") In the **Federal Register** of August 27, 1975 (40 FR 38179) a notice supplemented the original notice with a detailed, but not necessarily all inclusive, list of ingredients in miscellaneous external drug products to be considered in the OTC drug review. The list, which included "baby cream (diaper rash, rash, prickly heat);" "poision ivy and oak remedies;" "cold sore, fever blister;" "astringents (styptic pencil)," "astringents," and "wet dressing;" and "insect bites" active ingredients, was provided to give guidance on the kinds of active ingredients for which data should be submitted. The notices of November 16, 1973 and August 27, 1975 informed OTC drug product manufacturers of their opportunity to submit data to the review at those times and of the applicability of the monographs from the OTC drug review to all OTC products.

Under § 330.10(a)(1) and (5), the Commissioner of Food and Drugs appointed the following Panel to review the information submitted and to prepare a report on the safety, effectiveness, and labeling of the active ingredients in these OTC miscellaneous external drug products:

William E. Lotterhos, M.D., Chairman

Rose Dagirmanjian, Ph. D.

Vincent J. Derbes, M.D. (resigned July 1976)

George C. Cypress, M.D. (resigned November 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 the 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 in this document its conclusions and recommendations on OTC drug products containing skin protectant ingredients for the treatment of diaper rash; for the prevention of poison ivy, oak, and sumac; for the treatment of fever blisters; as astringents; and as insect bite neutralizers. The Panel's findings on other categories of miscellaneous external drug products are being published periodically in the **Federal Register.**

The Panel was first convened on January 13, 1975 in an organizational meeting. Working meetings at which OTC drug products for the treatment of diaper rash were discussed were held on November 12 and 13, 1976; June 5 and 6, 1977; October 5 and 6, November 7 and 8, and December 14, 1980. Working meetings at which OTC drug products for the prevention of poison ivy, oak, and sumac were discussed were held on April 2 and 3, May 16 and 17, October 8 and 9, and November 12 and 13, 1976; January 14 and 15, April 3 and 4, June 5 and 6, August 5 and 6, and September 30 and October 1, 1977; October 5 and 6, November 7 and 8, and December 14 and 15, 1980. Working meetings at which OTC drug products for the treatment of fever blisters were discussed were held on October 5 and 6, November 7 and 8, and December 14, 1980. Working meetings at which OTC astringent drug products were discussed were held on September 28 and 29, and November 9 and 10, 1975; May 16 and 17, June 11 and 12, and October 8 and 9, 1976; February 27 and 28 and December 11 and 12, 1977; June 11 and 12, August 11 and 12, and October 29 and 30, 1978; May 18 and 19, and September 28 and 29, 1979; August 3 and 4, October 5 and 6, November 7 and 8, and December 14 and 15, 1980. Working meetings at which OTC insect bite neutralizer drug products were discussed were held on October 8 and 9, and November 12 and 13, 1976; April 3 and 4, and June 5 and 6, 1977; October 5 and 6, November 7 and 8, and December 14 and 15, 1980.

The minutes of the Panel meetings are on public display in the Dockets Management Branch (HFA–305), Food and Drug Administration (address above).

No individuals requested to appear before the Panel to discuss skin protectant ingredients contained in drug products used for the treatment of diaper rash; for the prevention of poison ivy, oak, and sumac; for the treatment of fever blisters; or as insect bite neutralizers, nor was any individual requested to appear by the Panel.

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 astringent drug products:

Steven Carson, Ph. D.
Edward Jackowitz
James Leyden, M.D.
Kenneth Klippel
Robert Scheuplein, Ph. D.

No person who so requested was denied an opportunity to appear before the Panel to discuss astringent drug products.

The Panel has reviewed the literature and data submissions, and has considered all pertinent information submitted through December 14 and 15, 1980 in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations in § 330.10, the Panel reviewed the OTC drug products discussed in this document with respect to the following three categories:

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

Category II. Conditions under which OTC 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.

Referenced OTC Volumes

The "OTC Volumes" cited in this document include submissions made by interested persons in response to the call-for-data notices published in the **Federal Register** of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179). All of the information included in these volumes, except for those deletions which are made in accordance with confidentiality provisions set forth in § 330.10(a)(2), will be put on public display after October 7, 1982, in the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

I. Statement on OTC Drug Products for the Treatment of Diaper Rash

A. 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 baby cream (diaper rash, rash, prickly heat) active ingredients. Fifty ingredients were identified as follows: alkyldimethyl benzylammonium chloride, allantoin (5-ureidohydantoin), aluminum acetate, aluminum hydroxide, amylum, balsam peru, benzethonium chloride, benzocaine, bicarbonate of soda, bismuth subnitrate, boric acid, calamine, calcium carbonate, camphor, casein, cod liver oil, cysteine hydrochloride, dibucaine, diperodon hydrochloride, glycerin, hexachlorophene, 8-hydroxyquinoline, iron oxide, lanolin, menthol, methapyrilene, methionine, methylbenzethonium chloride, oil of eucalyptus, oil of lavender, oil of peppermint, oil of white thyme, panthenol, *para*-chloromercuriphenol, petrolatum, phenol, pramoxine

hydrochloride, salicylic acid, silicone, sorbitan, monostearate, talc, tetracaine, vitamin A, vitamin A palmitate, vitamin D, vitamin D_2, vitamin E, white petrolatum, zinc oxide, and zinc stearate. 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 drug products for the treatment of diaper rash.

1. *Submissions.* Pursuant to the above notices, the following submissions were received:

Firms	Marketed products
Block Drug Co., Inc., Jersey City, NJ 07302.	Tashan Super Skin Cream.
Bristol-Myers Col., New York, NY 10022.	Ammens Powder.
Chesebrough-Pond's, Inc., Trumbull, CT 06611.	Vaseline Pure Petroleum Jelly.
Cooper Laboratories, Inc., Cedar Knolls, NJ 07927.	Aveeno Colloidal Oatmeal.
Corona Manufacturing Co., Atlanta, GA 30301.	Corona Ointment.
Macsil, Inc., Philadelphia, PA 19125.	Balmex Ointment.
Miles Laboratories, Inc., Elkhart, IN 46514.	Acid Mantle Creme, Acid Mantle Lotion.
DPennwalt Corp., Rochester, NY 14603.	Caldesene Powder, Caldesene Ointment, Proposed Product Containing Calcium Undecylenate and Hydrocortisone Acetate.
Pfizer Pharmaceuticals, New York, NY 10017.	Desitin Ointment.
Resinol Chemical Col., Baltimore, MD 21201.	Resinol Ointment, Resinol Greaseless Cream.
Sterling Drug, Inc., New York, NY 10016.	Diaparene Ointment, Diaparene Peri Anal, Diaparene Baby Lotion, Diaparene Medicated Baby Powder, Diaparene Diaper Rinse Solution, Diaparene Diaper Rinse (Tablets), Diaparene Diaper Rinse (Granules).
Stiefel Laboratories, Inc., Oak Hill, NY 12460.	Zeasorb Super Absorbent Medicated Powder.
Syntex Laboratories, Inc., Palo Alto, CA 94304.	Methakote Diaper Rash Cream.
The Upjohn Co., Kalamazoo, MI 49001..	Clocream Skin Cream.
USV Pharmaceutical Corp., Tuckahoe, NY 10707.	Panthoderm Cream, Panthoderm Lotion.
Whitehall Laboratories, Inc., New York, NY 10017.	Sperti Healing Ointment.
Warren-Teed Pharmaceuticals, Inc., Columbus, OH 43215.	Taloin Diaper Rash Ointment.

2. *Related submissions.* The Panel received data on the role of corn starch as a nutrient for *Candida albicans* from the Department of Dermatology, University of Pennsylvania. Data on the safety of 100 percent corn starch as a dusting powder and an evaluation of the effectiveness of methylbenzethonium chloride in diaper rash remedies were received from Glenbrook Laboratories (a Division of Sterling Drug, Inc.).

3. *Ingredients.* The following list contains ingredients in marketed products submitted to the Panel or ingredients that appeared in the call-for-data notice pulished in the **Federal Register** of August 27, 1975 (40 FR 38179):

Alkyldimethyl benzylammonium chloride
Allantoin (5-ureidohydantoin)
Aluminum acetate
Aluminum hydroxide
Aluminum dihydroxy allantoinate
Amylum
Aromatic oils
Balsam peru
Balsam peru oil
Beeswax
Benzethonium chloride
Benzocaine
Bicarbonate of soda
Bismuth subcarbonate
Bismuth subnitrate
Boric acid
Calamine (prepared calamine)
Calcium carbonate
Calcium undecylenate
Camphor
Casein
Cellulose
Chloroxylenol (*p*-chloro-*m*-xylenol)
Cod liver oil
Corn starch
Cysteine hydrochloride
Dexpanthenol (*D*-panthenol)
Dibucaine
Diperodon hydrochloride
Eucalyptol
Glycerin
Hexachlorophene
Hydrocortisone acetate
8-Hydroxyquinoline
Iron oxide
Lanolin
Live yeast cell derivative
Magnesium carbonate
Menthol
Methapyrilene
Methionine
DL-Methionine
Methylbenzethonium chloride
Microporous cellulose
Mineral oil
Oil of cade
Oil of eucalptus
Oil of lavender
Oil of peppermint
Oil of white thyme
Panthenol
Para-chloromercuriphenol
Petrolatum
Phenol
Phenylmercuric nitrate
Pramoxine hydrochloride
Protein hydrolysate (composed of *L*-leucine, *L*-isoleucine, *L*-methionine, *L*-phenylalanine, and *L*-tyrosine)
Resorcinol (resorcin)
Salicylic acid
Shark liver oil
Silicone
Sorbitan monostearate
Starch
Talc
Tetracaine
Vitamin A
Vitamin A palmitate
Vitamin D
Vitamin D_2
Vitamin E (*DL-alpha*-tocopheryl acetate)
White petrolatum
Zinc oxide
Zinc stearate

B. General Discussion

The Panel has determined that many of the ingredients contained in products with "diaper rash" claims submitted to this Panel (Ref. 1), or labeling claims related to diaper rash (skin irritation), have previously been reviewed by other OTC advisory review panels. In this statement, the Panel presents some general comments on OTC drug products for the treatment of diaper rash.

In the **Federal Register** of August 4, 1978 (43 FR 34628), FDA published a proposed monograph (advance notice of proposed rulemaking) on OTC skin protectant drug products used as absorbents, adsorbents, astringents, demulcents, emollients, lubricants, and wound-healing aids. The Miscellaneous External Panel believes that the use of these products to provide mechanical or physical protection may prevent further skin irritation associated with diaper rash. Furthermore, the Panel notes that the ingredients allantoin (5-ureidohydantoin), aluminum hydroxide, bicarbonate of soda, bismuth subnitrate, boric acid, calamine (prepared calamine), corn starch, glycerin, live yeast cell derivative, petrolatum, shark liver oil, white petrolatum, and zinc oxide are included in the skin protectant rulemaking and, therefore, recommends that the use of these ingredients for "diaper rash" be referred to that rulemaking.

The Panel recommends that the other ingredients listed above be referred to the rulemaking(s) that FDA considers most appropriate.

Note.—In order to assure that these ingredients are referred to the most appropriate rulemakings, FDA is seeking public comment from any interested person. Written comments should be submitted in the manner described at the end of this document.

The Panel also recommends that FDA develop labeling for diaper rash drug products by reviewing the Category I labeling already developed in other rulemakings for possible modification to include "diaper rash."

Note.—Elsewhere in this issue of the **Federal Register**, the Panel's statement on OTC drug products for the treatment of diaper rash is included in the rulemakings for topical antifungal drug products, topical antimicrobial drug products, and external analgesic drug products.

The Panel further notes that hexachlorophene is included in the above list of ingredients. However, the use of hexachlorophene as a component

of OTC drug products is restricted by 21 CFR 250.250(d). Hexachlorophene is limited to situations where an alternative preservative has not yet been shown to be as effective or where adequate integrity and stability data for the reformulated product are not yet available. Use of hexachlorophene as a preservative at a level higher than 0.1 percent is regarded as a new drug use requiring an approved new drug application.

The Panel did not review any individual ingredients. Instead, the Panel presents the following general comments on the use of OTC diaper rash drug products.

Diaper rash is a common skin problem of infancy, caused by contact with urine and feces, worsened by occlusion with plastic pants, and often secondarily infected with *Candida albicans*. It has an excellent prognosis for permanent cure after an infant is toilet trained. Incontinent adults may get similar irritant contact dermatitis.

The skin under the diaper is macerated by prolonged wetness. Disposable diapers with a plastic backing, or plastic pants used over regular diapers, keep heat as well as moisture in, causing miliaria (prickly heat) as well as more maceration than occurs with the use of regular diapers alone. Bacteria proliferate in this warm, moist environment, thriving on nutrients in feces and metobolizing urine to produce ammonia, an irritant. *Candida Albicans*, often present in feces, also proliferates to produce a characteristic bright red, sharply marginated rash with satellite pustules and erosions. Other exacerbating factors are diarrhea, heat, mechanical irritation (chafing) from rough cloth or tight or stiff plastic, and chemical irritation from detergent and bleach in diapers or from soap used to cleanse the baby.

Ordinary mild diaper rash, characterized by erythema of the buttocks, perineum, and lower abdomen, responds to very frequent diaper changes, cleansing with water, and removal of plastic occlusion (switching to cloth diapers, often two at the same time). Most treatments help by protecting the skin, acting as a physical barrier to irritants, and absorbing or adsorbing moisture. Examples are talc and zinc oxide ointment and paste.

The Panel wishes to point out that physicians treat severe diaper rash with topical antifungal and anticandidal drugs such as iodochlorhydroxyquin, nystatin, amphotericin B, miconazole nitrate, and clotrimazole, often in combination with a topical steroid (Refs. 2 and 3). Potent fluorinated steroids, such as 0.1 percent triamcinolone cream, should not be used on diaper rash because when applied under occlusive dressing these steroids can produce local thinning of the skin, with striae and easy bruising, but 0.5 to 1 percent hydrocortisone cream is recommended.

References

(1) OTC Volumes 160021, 160025, 160027, 160028, 160038, 160040, 160041, 160042, 160053, 160067, 160069, 160070, 160077, 160088, 160091, 160104, 160204, 160236, 160242 through 160247, 160271, 160272, 160277, 160357, 160362, and 160427.

(2) Weston, W. L., "Practical Pediatric Dermatology," Little, Brown and Co., Boston, pp. 51–53, 1979.

(3) Weinberg, S., and R. Hoekelman, "Pediatric Dermatology for the Primary Care Practitioner," McGraw Hill, New York, p. 121, 1979.

II. Statement on OTC Drug Products for the Prevention of Poison Ivy, Oak, and Sumac

A. 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 active ingredients in poison ivy and oak remedies. Forty-six ingredients were identified as follows: Alcohol, allantoin (5-ureidohydantoin), beechwood creosote, benzethonium chloride, benzocaine, benzyl alcohol, bicarbonate of soda, bichloride of mercury, bithionol, calamine, camphor, cetyldimethylbenzylammonium chloride, chloral hydrate, chloroform, chlorpheniramine maleate, dimethyl polysiloxane, diperodon hydrochloride, diphenhydramine hydrochloride, endothermic hectorite, ferric chloride, glycerin, hexachlorophene, hydrogen peroxide, hydrous zirconia, iron oxide, isopropyl alcohol, lanolin, lead acetate, lidocaine, menthol, merbromin, oil of eucalyptus, oil of turpentine, panthenol, parethoxycaine, phenol, phenyltoloxamine dihydrogen citrate, polyvinyl pyrrolidone, pyrilamine maleate, salicylic acid, tannic acid, tincture of impatiens bi-flora, triethanolamine, zinc acetate, zirconium oxide, and zyloxin. 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 poison ivy and oak remedy drug products.

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

Firms	Products
Marion Health and Safety, Inc., Rockford, IL 61101.	Poison Ivy Wash, Ferric Chloride, and Zircreme.
Unimed, Inc., Somerville, NJ 08876.	Residerm.

B. Classification of Ingredients

In this document, the Panel has reviewed only those ingredients with a claim for preventing poison ivy, oak, or sumac.

1. *Active ingredients.* Buffered mixture of cation and anion exchange resins.

2. *Other ingredient.* The Panel was not able to locate nor is it aware of data demonstrating the safety and effectiveness of ferric chloride when used as an OTC poison ivy, oak, and sumac prevention active ingredient. The Panel, therefore, classifies ferric chloride as Category II for this use, and it will be briefly discussd later in this document. (See part II. paragraph C. below—*General Discussion.)*

3. *Ingredients deferred to other rulemakings.* The Panel has determined that some of the ingredients that appeared in the **Federal Register** of August 27, 1975 (40 FR 38179) are contained in products usually associated with the symptomatic treatment of poison ivy, oak, and sumac. These types of products have been previously reviewed by the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products as skin protectant drug products (for symptoms of oozing or weeping due to contact dermatitis, poison oak, or poison ivy) in the **Federal Register** of August 4, 1978 (43 FR 34628).

Note.—Elsewhere in this issue of the **Federal Register**, the Panel's statement on OTC drug products for the prevention of poison ivy, oak, and sumac is included in the rulemaking for external analgesic drug products.

The Panel did not receive any data on the following ingredients used for the prevention of poison ivy, poison oak, and poison sumac. These ingredients should be considered in other appropriate rulemakings for their use in treating poison ivy, poison oak, poison sumac, and their related symptoms.

Alcohol
Allantoin
Benzethonium chloride
Benzocaine
Benzyl alcohol
Bithionol
Calamine
Camphor
Cetalkonium chloride (cetyldimethylbenzylammonium chloride)
Chloral hydrate

Chlopheniramine maleate
Creosote (beechwood creosote)
Diperodon hydrochloride
Diphenhydramine hydrochloride
Endothermic hectorite
Eucalyptus oil (oil of eucalyptus)
Glycerin
Hydrogen peroxide
Iron oxide
Isopropyl alcohol
Lanolin
Lead acetate
Lidocaine
Menthol
Merbromin
Mercuric chloride (bichloride of mercury)
Oil of turpentine
Panthenol
Parethoxycaine hydrochloride (parethoxycaine)
Phenol
Phenyltoloxamine citrate (phenyltoloxamine dihydrogen citrate)
Polyvinylpyrrolidone (polyvinyl pyrrolidone)
Pyrilamine maleate
Salicylic acid
Simethicone (dimethyl polysiloxane)
Sodium bicarbonate (bicarbonate of soda)
Tannic acid
Tincture of impatiens bi-flora
Trolamine (triethanolamine)
Zinc acetate
Zirconium oxide (hydrous zirconia)
Zyloxin

4. *Ingredients subject to existing regulation.* The Panel notes that hexachlorophene and chloroform are restricted as components of OTC drug products under 21 CFR 250.250(d) and 21 CFR 310.513.

C. General Discussion

The Panel received three submissions for products claiming to prevent poison ivy, oak, or sumac by complexing with the plant antigen before it enters the skin (Refs. 1, 2, and 3). Two submissions contained no substantial data to establish the safety and effectiveness of the active ingredient (ferric chloride) contained in the product (Refs. 2 and 3). The Panel has therefore placed this ingredient in Category II. (See paragraph B.2. above—Other ingredients.) The third submission (Ref. 1) contained data on the use of a buffered mixture of cation and anion exchange resins in the prevention and treatment of poison ivy. The Panel addresses these data below. (See part II. paragraph D.3.a. below—*Category III ingredient—Buffered mixture of cation and anion exchange resins.)*

The Panel wishes to emphasize that claims for the relief of minor skin irritations, itching, and rashes due to poison ivy, oak, and sumac have been previously addressed by another OTC Advisory Review Panel. (See the report on OTC External Analgesic Drug Products published in the **Federal Register** of December 4, 1979 (44 FR 69768).) Therefore, this document only discusses the use of OTC drug products for the prevention of poison ivy, oak, and sumac. The Panel recommends that the agency defer to other appropriate rulemakings those ingredients and labeling claims submitted for treatment of the symptoms of poison ivy, oak, and sumac.

References

(1) OTC Volume 160103.
(2) OTC Volume 160132.
(3) OTC Volume 160152.

D. Categorization of Data

1. *Category I conditions.* None.

2. *Category II conditions.* (See part II, paragraph B.2. above—*Other ingredient.*)

3. *Category III conditions.* These are conditions for which available data are insufficient to permit final classification at this time.

a. *Category III ingredient—Buffered mixture of cation and anion exchange resins.* The Panel concludes that there are insufficient data to establish the effectiveness of a buffered mixture of cation and anion exchange resins for the prevention of poison ivy, oak, and sumac.

This mixture is a resin bed that contains both acidic groups and basic groups, mixed intimately in definite ratios, and possesses the ability to remove cations and anions simultaneously from solution.

(i) *Safety.* Skin irritation studies submitted show insignificant degrees of irritation during the first 2 weeks of observation. During the fourth week of observation severe lesions with cellulitis were seen in the rabbit skin and the technician applying the test material. It was the conclusion of the investigators that the test material was safe for topical application if it were used for a period not exceeding 14 to 21 days (Ref. 1).

(ii) *Effectiveness.* The mechanism of action of the buffered mixture of anion and cation exchange resins is claimed to be that these ingredients react chemically with the plant irritants that cause poison ivy, oak, and sumac to inactivate them. The inactivated irritants can then be readily removed from the skin by washing. However, Fisher (Ref. 2) states that no topical measure is effective in preventing poison ivy dermatitis.

The data submitted included an unblinded, poison ivy efficacy study using 20 subjects to determine efficacy of the mixture and an unblinded, uncontrolled clinical study. The uncontrolled clinical study consisted of 32 case reports submitted by 13 different physicians who claimed effective results from the product.

Twenty male subjects, who were sensitive to poison ivy, were chosen for the unblinded study to evaluate the efficacy of a buffered mixture of cation and anion exhange resin in the treatment of poison ivy. Ten subjects followed a therapeutic course, and ten of the subjects followed a prophylactic course. For purposes of this document only, the portion of the study dealing with dermatitis prevention properties of the active ingredient is relevant. In this portion, the placebo showed almost the same degree of efficacy as the mixture of resins (Ref. 1).

(iii) *Evaluation.* The Panel concludes that there are insufficient data to show the effectiveness of a buffered mixture of anion and cation exchange resins when used in the prevention of poison ivy dermatitis.

References

(1) OTC Volume 160103.
(2) Fisher, A. A., "Contact Dermatitis," 2d Ed., Lea and Febiger, Philadelphia, pp. 260–265, 1973.

b. *Category III labeling.* None.

III. Statement on OTC Drug Products for the Treatment of Fever Blisters

A. 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 "cold sore, fever blister" active ingredients. Eighteen ingredients were identified as follows: alcohol, allantoin (5-ureidohydantoin), ammonia, ammonium carbonate, benzalkonium chloride, benzocaine, camphor, lanolin, lanolin alcohol, menthol, mineral oil, paraffin, peppermint oil, petrolatum, phenol, sorbitan sesquioleate, soya sterol, and tannic 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 "cold sore, fever blister" drug products.

1. *Submissions.* Pursuant to the above notices, the following submissions were received:

Firms	Marketed products
Blistex, Inc., Oak Brook, IL 60521	Blistex Ointment, Blistik Medicated Lip Balm.
Campbell Laboratories, Inc., Farmingdale, NY 10022.	Herpecin-L.
Commerce Drug Co., Inc., Farmingdale, NY 11735.	Bio-Stik, Tanac Stik, Tanac.

Firms	Marketed products
International Pharaceutical Corp., Kansas City, MO 64114.	Gly-Oxide.
Oral Prophylactic Association, Inc., Duluth, MN 5512.	Mouth Komfort.
Sterling Drug, Inc., New York, NY 10016.	Campho-Phenique.

2. *Ingredients.* The following list contains labeled ingredients contained in marketed products submitted to the Panel or ingredients that appeared in the call-for-data notice published in the **Federal Register** of August 27, 1975 (40 FR 38179):

Alcohol
Allantoin (5-ureidohydantoin)
Ammonia
Ammonium carbonate
Amyl Dimethyl-*p*-aminobenzoate
Amyl *para*-dimethylaminobenzoate
Anhydrous glycerol
Aromatic oily solution
Beeswax
Benzalkonium chloride
Benzocaine
BHA
Bismuth sodium tartrate
Calcium silicate
Camphor
Candlelillia wax
Carbamide peroxide
Carnauba wax
Castor oil
Cetyl alcohol
Escalol 506
Glycerol
Homosalate
Lanolin
Lanolin alcohol
Menthol
Mineral oil
Octyldodecanol
Ozokerite
Paraffin
Pectin
Peppermint oil
Petrolatum
Pheno
Propyl *p*-benzoate
Pyridoxine hydrochloride
Sorbitan sesquioleate
Soya sterol
Sesame oil
Spermaceti
Talcum powder
Tannic acid
Thymol
Titanium dioxide
Wheat germ glycerides
White petrolatum

B. General Discussion

The Panel has determined that many of the ingredients contained in products with "cold sore, fever blister" claims submitted to this Panel (Ref. 1), or labeling claims related to fever blisters (irritation and discomfort), have previously been reviewed by other OTC advisory review panels. In this statement, the Panel presents some general comments on OTC drug products for the treatment of fever blisters.

In the **Federal Register** of August 4, 1978 (43 FR 34628), FDA published a proposed monograph (advance notice of proposed rulemaking) on OTC drug products. The OTC drug products subject to this rulemaking include products used as absorbents, adsorbents, astringents, demulcents, emollients, lubricants, and wound-healing aids. The Miscellaneous External Panel believes that the use of these products may also be useful for the treatment of fever blisters. Furthermore, the Panel notes that the ingredients allantoin, glycerin, petrolatum, tannic acid, and white petrolatum are included in the skin protectant rulemaking and, therefore, recommends that the use of these ingredients for "fever blisters" be referred to that rulemaking.

The Panel recommends that the other ingredients listed above be referred to the rulemaking(s) that FDA considers most appropriate. (Note: In order to assure that these ingredients are referred to the most appropriate rulemaking(s), FDA is seeking public comment from any interested person. Written comments should be submitted in the manner described at the end of this document.) The Panel also recommends that FDA develop labeling for cold sore and fever blister drug products by reviewing the Category I labeling already developed in other rulemakings for possible modification to include "cold sore" and "fever blister" claims.

Note.—Elsewhere in this issue of the **Federal Register**, the Panel's statement on OTC drug products for the treatment of fever blisters is included in the rulemaking for external analgesic drug products.

The OTC remedies for treating fever blisters consist of internally taken (oral) and externally applied (topical) medications. Only those which are externally administered to the lips are considered in this document. Preparations to be taken internally have been considered by the Advisory Review Panel on OTC Miscellaneous Internal Drug Products and its recommendations were published in the **Federal Register** of January 5, 1982 (47 FR 502).

The Panel did not review any individual ingredients. Instead, the Panel presents the following general comments on the use of OTC externally applied cold sore and fever blister drug products.

"Fever blisters" and "cold sores" are common names for herpes simplex, an acute infestious disease caused by the filterable (capable of passing through filters) virus *Herpes simplex*, type 1. Herpes simplex viruses are deoxyribonucleic acid (DNA) viruses, sensitive to ethyl ether and of two antigenic types. The type 1 virus is usually, but not exclusively, associated with nongenital lesions. The usual site of the lesion is at the junction of the mucous membrane and skin on the lips or nose. Hence, the term *herpes labialis* is frequently used. Occasionally, the lesions may occur in the skin in various areas of the body. The virus is spread from person to person by the oral or respiratory route. One the other hand, the type 2 virus is usually, but not exclusively (a small percentage of fever blisters are caused by this type), associated with genital lesions and is spread from person to person by sexual contact. Hence, the term *herpes genitalis* is frequently used for this type of infection, which, at the present time, is perhaps the third most common sexually transmitted disease.

A description of the development of a herpes simplex lesion provides the explanation why there are no adequate OTC measures currently available for specifically preventing or curing the infection. The assemblying of the virus capsid within the nucleus of an infected cell is the beginning of virus production. The envelope is assembled around the capsid when it passes through the membrane of the nucleus into the cytoplasm of the host cell. Later the virus is released from the host's cell. Thus it is believed that any locally applied drug is likely to be without direct action upon the intracellular virus and is not beneficial prophylactically or therapeutically.

The course of events during herpetic infections in man is well understood and occurs in a predictable order. The majority of adults have humoral immunity (antibodies) to the herpes simplex type 1 virus so the majority of infants are born with passive immunity comparable to the degree of active immunity of the mother. The inherited passive immunity of the infant disappears during the first few months of life and by about 5 years of age the child begins to develop active immunity by exposure to the virus. The first infection in the nonimmune individual due to exposure to the virus is designated primary herpes. It may be so mild as to be unnoticed, a subclinical infection, or it may be severe; the symptoms in the latter case may range from a severe localized infection to a generalized infection that occasionally is fatal.

Usually the primary herpetic infection in the nonimmune person manifests itself by vesicles (blisters) on the mucous membranes in the mouth. The gums and tonsils may be involved as well as the regional lymph nodes. There may be a constitutional reaction and higher fever. The virus may gain entrance to the blood stream that may result in a generalized vesicular eruption on the skin (a herpeticum eczema). The eyes may become involved, which results in a keratoconjunctivitis, and the central nervous system may become involved, giving rise to meningoencephalitis. Severe primary herpetic infections require laboratory procedures for specific diagnosis in order to differentiate them from infections with other viruses which may produce similar symptoms. Fortunately, the primary herpetic infection usually is self-limited. It persists longer than the recurrent infections, possibly 2 weeks, the period during which the body develops antibodies to combat the infection. The virus is not eliminated from the body with recovery from the primary infection. Once infected, an individual probably harbors the virus for the remainder of his or her lifetime. (Ref. 2).

During the intervals between the primary infection and the first recurrent infection, and between subsequent recurrent infections, the herpes virus is thought to remain dormant in the neurons of the sensory ganglia serving the region of the primary infection (a latent infection). The current thinking is that the incomplete virus may be integrated into the host cell chromosomes. In any event, the humoral and cellular immunities of the host keep the infection under control until some event occurs to reduce the immunity (resistance) of the host. Such events as fever, chilling, sunburn, windburn, menstruation, upset stomach or gastrointestinal disturbance, emotional stress, or excitement may reduce the immune state suficiently for the virus to become activated and again cause an infection, designated recurrent herpes (Ref. 2).

Recurrent herpes usually begins with a sensation of mild burning or itching and a feeling of firmness in the local area. Shortly thereafter, papules appear followed by vesicles. The sensation of firmness and the appearance of papules are due to the intra- and inter-cellular edema (accumulation of fluid). If erythema (redness) occurs in the area, it is due to the dilation of the blood capillaries. The vesicles may coalesce to form groups of thin-walled vesicles which may rupture. The vesicle fluid contains the complete virus and it is infectious. The stratum mucosum (prickle-cells) of the skin is involved and when the vesicles rupture and the overlying layers of the skin slough off, scabs form and healing takes place without scarring. If large denuded areas appear before scab formation occurs, bleeding may occur. If the scabs are large, cracking or separation may occur due to the movement of the lips. Necrosis does not occur. Occasionally, secondary bacterial infection may take place. Healing usually takes place in about 7 to 10 days. If healing does not take place within this time period, the consumer may have made a misdiagnosis of a fever blister and actually had something worse. Hence, the Panel recommends that labeling for fever blister drug products contain the warning "If the fever blister does not improve in one week, consult a doctor." Recurrent infections usually occur in the same general area. The only preventive measure is to avoid, where possible, the conditions that bring about activation of the virus, if such events are known and can be controlled (Ref. 2).

The Panel concludes that primary infections with herpes virus type 1 may be so mild as to go unnoticed or sufficiently serious as to require the attention of a physician. The recurrent herpetic infections are more annoying or embarrassing than they are serious. While these, too, may be sufficiently serious to justify the services of a physician, the recurrent local infections usually can be self-diagnosed and OTC preparations used for palliative or symptomatic treatment.

The Panel discussed a newly developed technique for evaluating herpes treatment (Ref. 3). This technique used a guinea pig model in which the immune system was stimulated by drying the herpes lesion. The quicker the drying of the herpes cell, the faster it can be controlled from spreading to surrounding epithelial cells. Once the spread of herpes is slowed, the antigen-antibody reaction starts to inactivate the herpes virus.

Astringents such as tannic acid have been used in products for the relief of fever blisters (Ref. 4). The Miscellaneous External Panel notes that the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products, in the **Federal Register** of August 4, 1978 (43 FR 34628), noted that tannic acid has little action on intact skin. When applied to abraded tissue, it precipitates a protein-tannate film that serves as a mechanical cover which may encourage bacterial growth under the protein-tannate crust (43 FR 34644). However, the Panel concludes that tannic acid in low concentrations applied to a small area such as a fever blister would be safe (Ref. 5), but the data submitted (Ref. 4) on the use of this ingredient in treating fever blisters are insufficient to establish effectiveness. Nevertheless, the Panel recommends that human studies be conducted because the use of astringents may be a rational treatment in shortening the healing time of fever blisters.

Only one human study (Ref. 6) was submitted to the Panel. The study employed carbamide peroxide 10 percent in anyhdrous glycerin and a control of anhydrous glycerin. According to the researchers, the medication provided highly dependable relief of pain (the chief complaint from subjects) and surprisingly frequent reduction in healing time.

There is no prophylactic OTC therapy of proven value. Vaccines are being evaluated and may be useful in the future. The repeated use of small pox inoculations has never been reliably shown to inhibit recurrent herpes simplex (Ref. 7).

Although most viral infections cannot be cured by OTC drugs, fever blisters should not be neglected. Local anesthetics can relieve pain, antibiotics can control secondary bacterial infections when they occur, and ointments (protectants) can soften crusts. Steroid hormone ointments are not recommended against infections and may spread the virus (Ref. 8). Drying agents such as alcohols, astringents, or skin protectant agents may be useful (Ref. 7).

References

(1) OTC Volumes 160008, 160012, 160013, 160048, 160096, 160136, 160177, 160197, 160213, 160218, and 160231.

(2) Dorsett, P. H., "Burrows Textbook of Microbiology," 21st Ed., W. B. Saunders Co., Philadelphia, pp. 972–989, 1979.

(3) Transcript of Proceedings of the Advisory Review Panel on OTC Miscellaneous External Drug Products, October 6, 1980, pp. 28–33.

(4) OTC Volume 160012.

(5) Transcript of Proceedings of the Advisory Review Panel on OTC Miscellaneous External Drug Products, November 8, 1980, p. 24.

(6) OTC Volume 160177.

(7) Arndt, K. A., "Manual of Dermatologic Therapeutics With Essentials of Diagnosis," 2d Ed., Little, Brown and Co., Boston, pp. 103–110, 1978.

(8) "Canker Sores and Fever Blisters," National Institute of Dental Research, DHEW Publication No. (NIH) 79–247.

IV. Statement on OTC Astringent Drug Products

A. 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 astringents, astringent (styptic pencil), and wet dressings active ingredients. Thirty-one ingredients were indentified as follows: acetone, alcohol 14 percent, aluminum acetate, aluminum chlorhydroxy complex, aluminum sulfate, ammonium alum, benzalkonium chloride, benzethonium chloride, boric acid, calcium acetate, camphor, cresol, cupric sulfate, ferric subsulfate, isopropyl alcohol, menthol, oxyquinoline sulfate, phenol, polyoxyethylene monolaurate, potassium alum, potassium ferrocyanide, silver nitrate, sodium diacetate, starch, talc, tannic acid, tannic acid glycerite, zinc chloride, zinc phenolsulfonate, zinc stearate, and zinc sulfate. 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 astringent drug products.

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

Firms	Marketed products
Commerce Drug Co., Inc., Farmingdale, NY 11735..	Tanac.
Cooper Laboratories, Inc., Cedar Knolls, NJ 07927..	Bur-Veen.
Cox Drugs, Asheville, NC 28803.....	Formula U.
The E. E. Dickinson Co., Essex, CT 06426..	Witch Hazel.
Dome Division, Miles Laboratories, Inc., West Haven, CT 06516..	Domeboro Effervescent Tablets, Domeboro Powder Packets.
Foxpharmacal, Inc., Ft. Lauderdale, FL 33310..	Secret Mirache.
R. L. Gaddy Co., Tallahassee, FL 32302..	Ez-It Medicated Foot Powder.
Humphreys Pharmacal, Inc., Rutherford, NJ 07070..	Witch Hazel.
Marion Laboratories, Inc., Kansas City, MO 64137..	Bluboro Powder.
Requa Manufacturing Co., Inc., Greenwich, CT 06830..	Aluminum Sulfate.
Sea Breeze Laboratories, Inc., Pittsburg, PA 15244..	Sea Breeze.
The Woltra Company, Inc., New York, NY 10011..	Mammoth Styptic Pencil, Styptic Pencil.

B. Ingredients Reviewed by the Panel

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

Alcohol
Alum
Aluminum acetate
Aluminum sulfate
Aromatics
Benzalkonium chloride
Benzocaine
Benzoic acid
Borax
Boric acid
para-tertiary-Butyl-*meta*-cresol
Calcium acetate
Camphor
Carbolic acid
Colloidal oatmeal
Eugenol
Gum camphor
Honey
Menthol
Modified Burow's solution
Oil of cloves
Oil of eucalyptus
Oil of peppermint
Oil of sage
Oil of wintergreen
Powdered alum
Starch
Talc
Tannic acid
Thymol
Witch hazel
Zinc oxide
Zinc stearate

2. *Other ingredients.* The following list contains ingredients that appeared in the call-for-data notice published in the **Federal Register** of August 27, 1975 (40 FR 38179) and were not contained in marketed products submitted to the Panel.

Acetone
Alcohol 14 percent
Aluminum chlorhydroxy complex
Ammonium alum
Benzethonium chloride
Cresol
Cupric sulfate
Ferric subsulfate
Isopropyl alcohol
Oxyquinoline sulfate
Phenol
Polyoxyethylene monolaurate
Potassium ferrocyanide
Silver nitrate
Sodium diacetate
Tannic acid glycerite
Zinc chloride
Zinc phenolsulfonate
Zinc sulfate

C. Classification of Ingredients

1. *Active ingredients.*

Alumium acetate (modified Burow's solution)
Aluminum sulfate
Witch hazel

2. *Tannic acid.* The Panel decided not to review tannic acid as an astringent, but will discuss this ingredient for use in the treatment of fever blisters. (See part III, above—STATEMENT ON OTC DRUG PRODUCTS FOR THE TREATMENT OF FEVER BLISTERS.) This decision was based on the fact that the only submission on tannic acid contained data and information for use in treating fever blisters (OTC Volume 160012). The Panel concluded that it is dangerous to use tannic acid as an astringent over large areas of the body because it precipitates protein which forms a protective coating over mucous membranes and abraded tissue and because the area under the coating is conducive for bacterial growth.

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 astringent active ingredients. The Panel, therefore, classifies these ingredients as Category II for this use, and they will not be discussed further in this document.

Acetone
Alcohol
Alcohol 14 percent
Alum (powdered alum)
Aluminum chlorhydroxy complex
Ammonium alum
Aromatics
Benzalkonium chloride
Benzethonium chloride
Benzocaine
Benzoic acid
Borax
Boric acid
para-tertiary-Butyl-*meta*-cresol
Calcium acetate
Camphor (gum camphor)
Collodial oatmeal
Cresol
Cupric sulfate
Eugenol
Ferric Subsulfate
Honey
Isopropyl Alcohol
Menthol
Oil of cloves
Oil of eucalyptus
Oil of peppermint
Oil of sage
Oil of wintergreen
Oxyquinoline sulfate
Phenol (carbolic acid)
Polyoxyethylene monolaurate
Potassium alum
Potassium ferrocyanide
Silver nitrate
Sodium diacetate
Starch
Talc
Tannic acid glycerite
Thymol
Zinc chloride
Zinc oxide
Zinc phenolsulfonate
Zinc stearate
Zinc sulfate

D. General Discussion

The Panel has determined that some of the ingredients contained in products with "astringent" claims submitted to this Panel (Ref. 1), or labeling claims related to astringent use, have previously been reviewed by other OTC advisory review panels.

In the **Federal Register** of August 4, 1978 (43 FR 34628), FDA published an advance notice of proposed rulemaking on OTC skin protectant drug products. The OTC drug products subject to this rulemaking include products used as absorbents, adsorbents, astringents, demulcents, emollients, lubricants, and wound-healing aids. The Miscellaneous External Panel believes that the astringents discussed in this statement may also be useful to provide mechanical or physical protection that may prevent further skin irritation. Therefore, the Panel recommends that the astringent ingredients listed above be referred to the skin protectant rulemaking. (Note: In order to assure that these ingredients have been referred to the most appropriate rulemaking, FDA is seeking public comment from any interested person. Written comments should be submitted in the manner described at the end of this document.) The Panel also recommends that FDA review the Category I labeling recommended in this document and the Category I labeling already developed for astringents in other rulemakings. (Note: Elsewhere in this issue of the **Federal Register**, the Panel's recommendations on OTC astringent drug products are included in the rulemaking for external analgesic drug products. The Panel presents a discussion of aluminum acetate, aluminum sulfate, and witch hazel and also presents the following general comments on astringents.

The skin which covers the body is often subjected to injuries. Astringents are locally applied protein precipitants which have such a low cell penetrability that the action is essentially limited to the cell surface and the interstitial spaces. The permeability of the cell membrane is reduced, but the cells remain viable. The astringent action is accompanied by contraction and wrinkling of the tissue and by blanching. The cement substance of the capillary endothelium is hardened, thus pathological transcapillary movement of plasma protein is inhibited and local edema, inflammation, and exudation are thereby reduced. Mucus and other secretions therefore may be reduced; thus the affected area becomes drier (Ref. 2).

Astringents are employed therapeutically to arrest hemmorrhage by coagulating blood and to check diarrhea, reduce inflammation of mucous membranes, promote healing, toughen the skin, or decrease sweating. The mechanism of action by which astringents are thought to decrease sweating is to coagulate protein in the sweat ducts and also by causing a peritubular irritation that results in duct closure. Styptics are substances not especially related to the clotting mechanism but are capable of promoting clotting by precipitating proteins.

There are several varied definitions for astringents. Webster (Ref. 3) defines astringent as a medicine for checking the discharge of mucus or serum by causing shrinkage of tissue and also as a liquid cosmetic for cleansing the skin and contracting trhe pores. Dorland (Ref. 4) defines astringent as causing contracting, usually locally, after topical application. Based on standard tests, and wishing to standardize the definition, the panel has adopted the definition of an astringent as a substance which checks oozing, discharge, or bleeding when applied to the skin or mucous membrane and works by coagulating protein.

The principal astringents are (1) the salts of aluminum, zinc, manganese, iron, and bismuth; (2) certain other salts that contain these metals such as permanganates; and (3) tannins, or related polyphenolic compounds. Acids, alcohols, phenols, and other substances that precipitate proteins may be astringent in the appropriate amount or concentration; however, such substances generally are not employed for their astringent effects because they readily penetrate cells and promote tissue damage. Strongly hypertonic solutions dry the affected tissues and are thus often but wrongly called astringents, unless protein precipitation also occurs (Ref. 2).

References

(1) OTC Volumes 160022, 160038, 160039, 160069, 160070, 160093, 160140, 160219, 160230, 160233, 160354, 160396, 160409, 160413, 160428, 160429, 160433, and 160435.

(2) Harvey, S. C., "Topical Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by J. Hoover, Mack Publishing Co., Easton, PA, pp. 716–717, 1975.

(3) "Webster's Third New International Dictionary," edited by P. B. Gove, G. and C. Merriam Co., Springfield, MA, 1971, s.v. "astringent."

(4) "Dorland's Illustrated Medical Dictionary," 25th Ed., W. B. Saunders, Philadelphia, 1965, s.v. "astringent."

E. Categorization of Data

1. *Category I conditions.* The following are Category I conditions under which OTC astringent drug products are generally recognized as safe and effective and not misbranded.

Category I active ingredients. Aluminum acetate, Witch hazel.

(1) *Aluminum acetate.* The Panel concludes that aluminum acetate is safe and effective for OTC use as an astringent active ingredient in OTC topical drug products when used within the concentration specified below.

Aluminum acetate solution is classified as an astringent for topical use on the skin and mucous membranes (Ref. 1). It has been used by dilution with 10 to 40 parts of water as a wet dressing. The solution may be stabilized by the addition of not more than 0.6 percent of boric acid, and it must be dispensed only as a clear solution (Ref. 2).

Aluminum acetate solution has been referred to for years as Burow's solution, named from a similar mixture often prescribed by Dr. August Burow. In preparing aluminum acetate solution, various methods can be employed to produce aluminum acetate. Aluminum acetate solution can be prepared by adding 545 milliliters (mL) aluminum subacetate solution to 15 mL glacial acetic acid and adding sufficient water to make 1,000 mL (Ref. 1). Aluminum subacetate solution is prepared by mixing 145 grams (g) of aluminum sulfate with 160 mL acetic acid and 70 g of precipitated calcium carbonate and sufficient water to make 1,000 mL. Previously aluminum acetate had been prepared by dissolving 150 g of lead acetate and 87 g of aluminum sulfate in water. However, this method of preparation has been abandoned. In order for the finished product to meet the compendial standards for strength, quality, and purity, each 100 mL should yield 4.8 to 5.8 g of aluminum acetate (Ref. 2).

(i) *Safety.* Concentrated solutions of aluminum salts have produced gingival necrosis, hemorrhagic gastroenteritis, clonic contractions, and evidence of nephritis. The acute oral LD_{50} of aluminum sulfate, a precursor to aluminum acetate, is 6.1 grams/kilogram (g/kg). Burow's solution is reported to be moderately irritating if mistakenly ingested (Refs. 3 and 4).

The degree of absorption of ingested aluminum and its related compounds is minimal (Ref. 5). The toxicity of aluminum is now considered to be low. Adverse effects appear due to inhalations of finely divided powders of aluminum oxide and metallic aluminum.

Driesbach (Ref. 6) states that no fatalities from aluminum salts have been reported in recent years. Gosselin et al. (Ref. 3) state the Burow's solution is slightly toxic with a probable lethal dose for humans of 5 to 15 g/kg. It is moderately irritating if ingested. Lansdown (Ref. 7) has shown some effect of aluminum compounds applied topically to the mouse, rabit, and pig skin. Epidermal changes consisting of

hyperplasia, microabscess formation, dermal inflammatory cell infiltration, and occasional ulceration were evident in all three species treated with aluminum chloride (10 percent), aluminum nitrate (10 percent), aluminum sulfate, aluminum hydroxide, or aluminum chlorhydrate.

(ii) *Effectiveness.* Many historical references are made to the effectiveness and use of aluminum acetate as an astringent wet dressing, compress, or soak for minor skin irritations due to allergies, insect bites, athlete's foot, poison ivy, swelling associated with minor bruises, and ulcerations of the skin. The studies reviewed in the literature and submissions may be classified as limited uncontrolled studies and testimonials supporting the use of aluminum acetate in diseases of the legs, eczema, varicose ulcers, acute cutaneous inflammation, various dermatoses, and other conditions. Aluminum acetate soaks are used for relief of acute irritation while treating plantar lesions of the foot (Ref. 8) (as a soak the patient begins soaking the treated foot (feet) three times a day) (Ref. 9). The solution can also be used as a wet dressing in the treatment of athlete's foot (Ref. 10). Moist compresses of Burow's solution are used to hasten healing of plantar perforation ulcers (Ref. 11).

Leyden (Ref. 12) induced a poison ivy dermatitis in six poison ivy sensitive volunteers. Forty-eight hours later a cell-mediated immune reaction was seen consisting of blisters which represented dermal cell necrosis. The blisters were treated with aluminum acetate 1:40 (2.5 percent), aluminum acetate 1:20 (5 percent), tap water, or saline compresses. Leyden found no significant difference in aluminum acetate 1:40 compared to tap water compresses, but did find aluminum acetate 1:20 compresses superior to both the tap water compresses and saline compresses.

Based on the current literature and wide clinical usage, the Panel concludes that aluminum acetate solution 1:20 to 1:40 is safe and effective for topical use as an astringent.

(iii) *Dosage.* Topical dosage is a solution containing 2.5 to 5 percent aluminum acetate.

(iv) *Indications.* "For use as a wet dressing, compress, or soak for relief of inflammatory conditions and minor skin irritations due to allergies, insect bites, athlete's foot, poison ivy, or swelling associated with minor bruises and ulcerations of the skin."

(v) *Warnings.* (*a*) "If condition worsens or symptoms persist for more than 7 days, discontinue use of the product and consult a doctor."

(*b*) "Do not cover wet dressings or compresses with plastic to prevent evaporation."

(*c*) "Keep away from eyes."

(*d*) "For external use only."

(*e*) "Store in a cool dry place."

(vi) *Directions.* (a) Depending on the formulation and concentration of the marketed product, the manufacturer must provide adequate directions so that the resulting solution to be used by the consumer contains 2.5 to 5 percent aluminum acetate.

(b) *For products containing aluminum acetate for use as a soak.* "Soak affected area for 15 to 30 minutes. Repeat 3 times a day" (Ref. 9).

(c) *For products containing aluminum acetate for use as a compress or wet dressing.* "Saturate a clean, soft, white cloth (such as a diaper or torn sheet) in the solution, gently squeeze, and apply loosely to the affected area. Saturate the cloth in the solution every 15 to 30 minutes and apply to the affected area. Repeat as often as necessary. Discard remaining solution after use" (Ref. 13, 14, and 15).

References

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(8) Khoure, R. R., et al., "Verrucous Carcinoma of the Foot," *Journal of the American Podiatry Association,* 69:327–328, 1980.

(9) Shapiro, L. J., "Oblique Displacement Osteotomy for Correction of Hallux Adducto Valgus," *Current Podiatry,* 29:13–15, 1980.

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(12) Presentation by J. Leyden to the Advisory Review Panel on OTC Miscellaneous External Drug Products contained in the Transcripts of the Proceedings of its 42d meeting, pp. 7–18, November 7, 1980.

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(14) Combes, F. C., "The Wet Dressing, Its Use in Acute Cutaneous Inflammation," *Industrial Medicine and Surgery,* 30:29–34, 1961.

(15) Parker, G. F., and P. C. Logan, "Poison Ivy (Rhus) Dermatitis," *American Family Physician,* 6:62–66, 1972.

(2) *Witch hazel.* The Panel concludes that witch hazel (witch hazel water or hamamelis water) is safe and effective for OTC use as an astringent active ingredient on OTC topical drug products when used within the concentration specified below.

Witch hazel is a clear, colorless liquid having a characteristic odor and taste and is neutral or slightly acid to litmus paper (Ref. 1). It is prepared by macerating recently cut and partially dried dormant twigs of *Hamamelis virginiana* for about 24 hours in about twice their weight of water and then distilling until 850 mL of distillate is obtained from each 100 g. To each 850 mL distillate, 150 mL alcohol is added. Witch hazel contains 14 to 15 percent alcohol. It contains only a trace of volatile oils (0.01 to 0.02 percent) (Ref. 2). The tannin of witch hazel bark on distillation remains in the residue and is absent from the distilled extract (Refs. 2 and 4 through 12). Witch hazel has not been recognized in an official compendia since 1960 (Refs. 1 and 3).

(i) *Safety.* Aside from the slight stinging sensation, which has been attributed to the alcohol content (Ref. 9), no other reports of adverse effects to witch hazel have been found in the available medical literature. However, because witch hazel contains minute amounts of volatile oils, an allergic contact dermatitis is possible and cannot be discounted, although the occurance is rare (Refs. 2 and 12).

The Panel concludes that witch hazel can be used safely OTC, based on its use since the days of the early Colonists who learned of the drug from the American Indians (Ref. 3).

(ii) *Effectiveness.* Literature reports have attributed the astringent action of witch hazel to its tannin content (Refs, 4, 8, 11, 13, and 14). This tannin is hamamelitannin (Ref. 15), a catechol tannin (Ref. 3). One major manufacturer of witch hazel (which makes its produc from a distillate of a combination of th

witch hazel bark and leaf) states that the tannin concentration of hamamelitannin falls between 2.5 and 4.2 milligrams/liter (mg/L) (Ref. 16), which is considered to be a range of concentrations effective for use as an OTC astringent drug product. It may also be probable, but is not documented, that the astringent effect is due to the alcohol present in witch hazel. The same manufacturer maintains that even though alcohol is an astringent by itself, and enhances the action of the witch hazel distillate, its purpose for being in the product is only as a preservative (Ref. 16). Assumptions that the effectiveness of witch hazel is due to the small amount (0.01 to 0.02 percent) of volatile oils present have not been scientifically validated (Ref. 2).

Studies to show that witch hazel is an effective astringent have been done. One study shows that witch hazel shortened the bleeding time and accelerated the blood clotting in rabbits (Ref. 2), which may be related to the astringency effects of witch hazel. Another study was performed using the plasma recovered from six human blood samples. Duplicate prothrombin (clotting) times were done using the undiluted plasma (0.1. mL plus 0.1 mL normal saline) and 0.1 mL of three test samples—witch hazel containing 14 percent ethyl alcohol, 14 percent ethyl alcohol alone, and undiluted witch hazel. The study showed that the witch hazel alone was superior to the witch hazel containing 14 percent ethyl alcohol, and that both were superior to the 14 percent ethyl alcohol alone, in accelerating the clotting time of the human plasma (Ref. 17).

The popularity of witch hazel and its use by consumers and the medical profession may be attributed, as mentioned above, to the trace amount of volatile oils which gives the product a characteristically pleasant odor (Ref. 18). One major manufacturer maintains that its popularity is due to the astringent action provided by the significant amounts of natural hamamelitannin found in the witch hazel distillate. Hamamelitannin is one of a broad class of tannins. Tannins are classified as astringents due to their action when applied to living tissue. They precipitate proteins making that area resistant to the action of proteolytic enzymes. For example, when tannins (either purified or a derivative) are applied to abraded tissue, the proteins of the exposed tissues precipitate, forming a mildly antiseptic, protective coat allowing new tissues to grow underneath. According to data submitted by one manufacturer, witch hazel is effective in treating bruises, contusions, and sprains; for protecting slight cuts and scrapes; for relieving muscular pains; and for treating the pain and swelling of nonpoisonous insect bites (Ref. 19). Another manufacturer states that witch hazel has been used in the household for years as a local astringent for the treatment of bruises, skin irritations, sunburn, insect bites, and external hemorrhoids (Ref. 16). The Panel concludes that witch hazel is safe and effective as an OTC astringent drug product for external application.

(iii) *Dosage.* Topical dosage is witch hazel prepared according to National Formulary XI.

(iv) *Indications.* (*a*) "For use as an astringent for the treatment of bruises, contusions, and sprains."

(*b*) "For protecting slight cuts and scrapes."

(*c*) "For relieving muscular pains."

(*d*) "For treating the pain and swelling of insect bites."

(*e*) "For use as an astringent for the treatment of skin irritation, sunburn, and external hemorrhoids."

(v) *Warnings.* "For external use only."

(vi) *Directions.* "Apply as often as necessary."

References

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(16) OTC Volume 160428.

(17) OTC Volume 160433.

(18) Nesselrod, J. P., "Clinical Proctology," W. B. Saunders Co., Philadelphia, pp. 164–169, 1957.

(19) OTC Volume 160354.

2. *Category II conditions.* The following are Category II conditions under which OTC astringent drug products are not generally recognized as safe and effective or are misbranded.

a. *Category II ingredients.* (See part IV, paragraph C.3 above—*Other ingredients.*)

b. *Category II labeling.* The Panel has placed in Category II the following labeling claims because no data were submitted to establish safety and effectiveness of these claims:

(1) "For anthrax."

(2) "Lymphangitis."

3. *Category III conditions.* The following are Category III conditions for which available data are insufficient to permit the final classification of OTC astringent drug products at this time.

a. *Category III active ingredient—Aluminum sulfate.* The Panel concludes that aluminum sulfate is safe, but there are insufficient data to establish its effectiveness for use as a styptic pencil.

(1) *Safety.* Aluminum sulfate is generally recognized as safe and is utilized in food processing, brining pickles, baking powder, and clarifying fats and oils. It has been used as an ingredient in deodorant preparations. However, it has been shown to be deleterious to clothing.

The LD_{50} of aluminum sulfate has been determined to be 6.1 g/kg in mice by oral administration. Aluminum sulfate can cause a mild yet persistent irritation to the eyes, but it does not irritate the skin. When 200 human volunteers were patch tested, no visual irritation was observed on the arms or legs. By moistening a styptic pencil, containing approximately 57 percent aluminum sulfate and applying it to a cut, approximately 0.1 to 0.2 mL will be applied. This application will result in a local coagulation of capillary bleeding.

In 75 years of marketing styptic pencils there have been no reported instances of human toxicity (Ref. 1). However, application of the pencil on a cut may result in some stinging.

The Panel concludes that aluminum sulfate is safe for use as a styptic pencil.

(2) *Effectiveness.* Aluminum sulfate, when applied to minor cuts, acts as an astringent and a protein precipitant. The substance has little, if any, cell permeability and exerts its effect on the cell surface (Ref. 2). This effect has been elucidated over many years of use (Ref. 3).

Aluminum sulfate has been used widely for many years although modern day clinical trials have not been conducted with this ingredient.

The Panel concludes there are insufficient data to establish the effectiveness of aluminum sulfate as a styptic.

(3) *Indication.* "For use in stopping bleeding caused by minor surface cuts, particularly those caused during shaving."

(4) *Warnings.* (*i*) "For external use only."

(*ii*) "Do not use in or around eyes."

(5) *Directions.* "Moisten and apply. Dry after use."

References

(1) OTC Volume 160409.

(2) OTC Volume 160411.

(3) Harvey, S. C., "Topical Drugs," *in* "Remington's Pharmaceutical Sciences," 16th Ed., edited by A. Osol, Mack Publishing Co., Easton, PA, p. 721, 1980.

b. *Category III labeling.* None.

F. Combination Policy

The Panel is not aware of products combining OTC ingredients used as astringents for topical sue. The Panel is aware of products which combine various OTC ingredients with an astringent. Any such combination of ingredients reviewed in this document with ingredients from other therapeutic categories should meet the regulation outlined 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 ingredient 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.

Regarding combinations of ingredients for topical astringent use with ingredients from other therapeutic categories, the Panel also concurs with the FDA guidelines for OTC combination products (Ref. 1) which state that Category I active ingredients from different therapeutic categories may be combined to treat different symptoms concurrently only if each ingredient is present within its established safe and effective dosage range and the combination meets the OTC combination policy in all other respects.

Reference

(1) Food and Drug Administration, "General Guidelines for OTC Drug Combination Products, September 1978," Docket No. 78D–0322, Dockets Management Branch.

V. Statement on OTC Insect Bite Neutralizer Drug Products

A. Submission 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 insect bite active ingredients. Nineteen ingredients were identified as follows: alcohol, ammonium hydroxide, aqua ammonia, bicarbonate of soda, calamine, camphor, ethoxylated alkyl alcohol, ferric chloride, fluid extract ergot, menthol, obtundia surgical dressing, oil of turpentine, peppermint oil, phenol, pyrilamine maleate, sodium borate, triethanolamine, zinc oxide, and zirconium oxide. 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 insect bite drug products.

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

Firms	Products
Marion Health and Safety, Inc., Rockford, IL 61101.	Sting-Kill Swabs.
Tender Corp., Littleton, NH 03561	After Bite.

B. Ingredients Reviewed by the Panel

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

Benzalkonium chloride
Triethanolamine
Ammonium hydroxide

2. *Other ingredients,* The following list contains ingredients in OTC insect bite drug products, which appeared in the call-for-data notice published in the **Federal Register** of August 27, 1975, for which no marketed products were submitted to the Panel.

Alcohol
Aqua ammonia
Bicarbonate of soda
Calamine
Camphor
Ethoxylated alkyl alcohol
Ferric chloride
Fluid extract ergot
Menthol
Obtundia surgical dressing
Oil of turpentine
Peppermint oil
Phenol
Pyrilamine maleate
Sodium borate
Zinc oxide
Zirconium oxide

C. Classification of Ingredients

In this document, the Panel has reviewed only those ingredients with a claim for treating insect bites by neutralization or inactivation of insect venom.

1. *Active ingredients.*

Ammonium hydroxide
Triethanolamine

2. *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 insect bite neutralizer active ingredients. The Panel, therefore, classifies these ingredients as Category II for this use, and they will not be discussed further in this document.

Alcohol
Aqua ammonia
Benzalkonium chloride
Bicarbonate of soda
Calamine
Camphor
Ethoxylated alkyl alcohol
Ferric chloride
Fluid extract ergot
Methol
Obtundia surgical dressing
Oil of turpentine
Peppermint oil
Phenol
Pyrilamine maleate
Sodium borate
Zinc oxide
Zirconium oxide

D. General Discussion

Insect bites can be fatal to individuals who are hypersensitive to the antigenic substances in insect venom which precipitate anaphylactic shock. Immediate consideration should be given towards obtaining fast, appropriate emergency treatment. Because of the potential danger of cross sensitization to other antigenic substances, appropriate caution should be given to sensitive individuals. A program of desensitization should be implemented if at all possible.

For the majority of insect bites, the reactions are confined to varying degrees of itching and pain at the site of

the bite. Uncontrolled itching and pain often lead to scratching that can produce nodules and possibly secondary infections. The use of OTC products for relief of localized pain and itching can be helpful. Additional benefit may be achieved at times with the use of effective antibacterial agents and mild astringents. Ingredients and claims for the relief of minor skin irritation (which may result from insect bites) have previously been addressed by another OTC Advisory Review Panel. (See the report on OTC Skin Protectant Drug Products published in the **Federal Register** of August 4, 1978; 43 FR 34628.) Treatment of infectious diseases caused by insect bites is not within the realm of this Panel's deliberation.

E. Categorization of Data

1. *Category I conditions.* None.
2. *Category II conditions.* None.
3. *Category III conditions.* These are conditions for which available data are insufficient to permit final classification at this time.

a. *Category III ingredients.*

Ammonium hydroxide
Triethanolamine

(1) *Ammonium hydroxide.* The Panel concludes that ammonium hydroxide is safe but that there are insufficient data to establish its effectiveness as an insect bite neutralizer.

Ammonia is a colorless, transparent gas having a density approximately 0.6 that of air, an exceedingly pungent odor, and an acrid taste. Ammonia is very soluble in water. A portion of the dissolved ammonia gas reacts chemically with water to form ammonium hydroxide. Aqueous solutions of ammonia exhibit alkaline reaction, and have other properties similar to those of solutions of alkali hydroxides. These properties have been attributed to the ammonium hydroxide formed. Although there is little ammonium hydroxide formed, ammonia water is often referred to and labeled as solution of ammonium hydroxide (Ref. 1).

The ammonium ion is of particular interest because it is toxic in high concentrations and because it serves a major role in the maintenance of the acid-base balance of the body (Ref. 2).

(i) *Safety.* Ammonia is a naturally occurring product found abundantly in body tissues. Ammonia is absorbed by inhalation, ingestion, and probably percutaneously at concentrations high enough to cause skin injury. Data are not available on absorption of low concentrations through the skin. Once absorbed, ammonia is converted to the ammonium ion as the hydroxide and as salts, especially as carbonates. The ammonium salts are rapidly converted to urea, thus maintaining an isotonic system. Ammonia is also formed and consumed endogenously by the metabolism and synthesis of amino acids. Excretion is primarily by way of the kidneys, but a not insignificant amount is passed through the sweat glands (Ref. 3).

Patients with severe hepatic disease or with portacaval shunts often develop derangements of the central nervous system, which are manifested by disturbance of consciousness, tremor, hyperreflexia, and electroencephalogram abnormalities. Because this syndrome is most often associated with elevated concentrations of ammonia in blood, and because it can be provoked by feeding of protein as well as by ingestion of ammonium salts, it is thought to represent ammonia toxicity to the brain (Ref. 2).

The occurrence of high concentrations of ammonia in the blood (hyperammonemia) in children and infants has been associated with defects of enzymes of the urea cycle. Hyperammonemia due to defects of ornithine transcarbamylase or carbamylphosphate synthetase may be related to cyclic vomiting and to at least one form of migraine. The mechanisms by which ammonia induces changes in the central nervous system is not clear (Ref. 2).

Ammonia gas when inhaled in dilute form can stimulate the medullary respiratory and vasomotor centers reflexly through irritation of the sensory endings of the trigeminal nerve (Ref. 2).

The strong, pungent, penetrating odor of low levels of ammonia at about 35 milligrams per cubic meter (mg/m^3) becomes increasingly irritating as concentrations exceed 70 mg/m^3 (Ref. 3). High concentrations of ammonia vapor are injurious to the lungs, and death may result from pulmonary edema. Long exposure to low concentrations of ammonia may lead to chronic pulmonary irritation. The maximal concentration of ammonia vapor that can be tolerated without harmful effect is probably less than 250 parts per million (ppm). High concentrations of neutral ammonium salts are irritating to the gastric mucosa and may produce nausea and vomiting (Ref. 2).

Ammonia preparations used externally have been discussed in some current sources of chemical and pharmaceutical information (Refs. 4 and 5).

(2) *Effectiveness.* The local reaction that follows insect bites may vary among individuals. Mild local reaction may consist of itching, swelling, and irritation. Solutions of ammonium hydroxide are local irritants. When applied to the skin in low concentrations, they have a rubefacient action, and in high concentrations they are vesicant. Few authoritative publications provide information regarding optimum concentrations of ammonia in counterirritant products.

The venom of stinging insects (bees, wasps, hornets, and ants) and the substances released by biting insects (mosquitos, flies, fleas, bedbugs, ticks, and chiggers) are varied in chemical nature. These substances range from simple amines, such as histamine and 5-hydroxytrytamine, to more complex peptides, kinins, and enzymes, such as hyaluronidase and phospholipase, being both acidic and basic in nature. While some of the substances may be primarily acidic in nature, such as the formic acid injected from the bite of some ants, it is erroneous to expect that solely neutralizing the acids will lead to complete and effective relief of all insect stings or bites (Ref. 6). Therefore, the use of remedies which are alkaline and solely directed to neutralizing acids of stinging insect venoms or insect bites are not generally acceptable treatment at this time.

(3) *Evaluation.* The submitted data (Ref. 7) do not establish the effectiveness of ammonium hydroxide in neutralizing insect bites or stings. The Panel recommends Category III for effectiveness of ammonium hydroxide either alone or in combination for the neutralization of insect stings and bites.

References

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(4) Todd, R. G., "Martindale, The Extra Pharmacopeia," 27th Ed., The Pharmaceutical Press, London, pp. 44–45, 1977.

(5) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, N.J., p. 69, 1976.

(6) Sadik, F., "Insect Sting and Bite Products," *in* "Handbook of Nonprescription Drugs," 6th Ed., American Pharmaceutical Association, Washington, pp. 326–327, 1979.

(7) OTC Volumes 160119 and 160434.

(2) *Triethanolamine.* The Panel concludes that triethanolamine is safe but that there are insufficient data to establish its effectiveness as an insect bite neutralizer.

Triethanolamine is an organic base related to ammonia in which the three hydrogen atoms in the ammonia structure have been replaced by the ethanol group. An important physical property of triethanolamine is its complete solubility in water and many organic solvents. It is one of the most hygroscopic organic solvents available, and its high boiling point makes it less volatile when used alone or in combination. It has a low vapor pressure and is compatible with many materials. It is used as a mild alkaline hygroscopic agent, acid gas absorbent, penetrant solvent, dispersing agent, and as an intermediate in the preparation of emulsifying agents and other derivatives (Ref. 1).

(i) *Safety.* Evidence has been previously presented to the Panel that indicates that triethanolamine is relatively safe when ingested or administered orally to experimental animals. Its oral LD_{50} in the rat and guinea pig is in the 8-milligram-per-kilogram (mg/kg) range. Several ounces can be tolerated by humans according to Gosselin et al. (Ref. 2). The principal effect of triethanolamine has been limited to the gastrointestinal tract or to systemic alkalosis as a result of its alkalinity. While it can be absorbed when applied to the skin, little evidence exists to indicate that it is toxic to the skin in concentrations of 2.5 percent found in lotions, creams, or solutions, or in concentrations of 30 percent found in swabs. Because of its alkalinity, it may be irritating to the skin if applied in large concentrations for long periods of time.

(ii) *Effectiveness.* The use of triethanolamine in insect remedies may be related partly to its physical-chemical properties. It is alkaline in solution, with a pH between 10 and 11, and has been used as a binding agent, emulsifier, and solvent. However, it is emphasized that the rationale of using triethanolamine to neutralize acids from insect bites or stings is based on the erroneous assumption that acids are the sole causative agents in insect bites or stings.

In the data submitted (Refs. 1 and 3), triethanolamine is in combination with benzalkonium chloride. Triethanolamine is purported to be a strong alkalizing agent, neutralizing the antigens in the insect venom. The benzalkonium chloride is purported to be present as an antiseptic for the sting site. (The combination will not be discussed further as this report deals solely with the neutralization of insect bites.) The same double-blind clinical study is provided in both submissions, which cover the same product. Bee stings were simulated in 26 previously determined nonallergenic subjects by injecting 0.02 ml of a reconstituted lyophilized (freeze-dried) bee venom into the arms of each subject. When pain was sensed, a pair of swabs, one saturated with the test product and one saturated with a saline placebo and given in a double-blind fashion, was spread gently over the lesions, one on each arm.

The time for reduction of pain or its elimination was recorded. While some limitations exist in the quality of data generated to make definite statements regarding the time it took to achieve pain reduction or pain elimination, reevaluation of the data by an agency statistician indicated that the test product gave a faster response than did placebo. Specifically, the data support the claim that a large proportion, 13 of 26 (50 percent), of subjects experienced pain reduction or elimination within 120 seconds with the test product as compared to the number of subjects who experienced pain reduction or relief (6 of 26 or 23 percent) when given the placebo. The degree of erythema and edema (swelling) was not affected by either treatment.

(iii) *Evaluation.* Because no similar study nor demonstration of efficacy has been shown for triethanolamine as a single active ingredient in neutralizing insect bites, it is not possible to assess its contribution to the effectiveness of the product. Therefore, the Panel recommends Category III for effectiveness of triethanolamine, either alone or in combination, for the neutralization of insect stings or bites. The clinical study using artificially induced bee stings outlined above, while not in the report, could serve as a model by which single ingredients can be tested for effectiveness in the relief or elimination of pain or itch from insect bites or stings.

References

(1) OTC Volume 160159.

(2) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., The Williams and Wilkins Co., Baltimore, p. 73, 1976.

(3) OTC Volume 160074.

b. *Category III labeling.* "For the temporary relief of stings caused by wasps, hornets, bees, mosquitos, spiders, fleas, chiggers, ticks, and ants."

List of Subjects in 21 CFR Part 347

OTC drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 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), the agency advises in this advance notice of proposed rulemaking that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations would be amended in Part 347 (as set forth in the advance notice of proposed rulemaking for skin protectant drug products that was published in the **Federal Register** of August 4, 1978 (43 FR 34628)) as follows:

PART 347—SKIN PROTECTANT PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. In Subpart A, § 347.3 would be amended to include the following definition:

§ 347.3 Definitions.

* * * * *

Astringent. A drug product which checks oozing, discharge, or bleeding when applied to skin or mucous membrane and works by coagulating protein.

2. Subpart B would be amended by adding new § 347.12, to read as follows:

§ 347.12 Astringent active ingredients.

The active ingredient of the product consists of the following within the specified concentration:

(a) Aluminum acetate, 2.5 to 5 percent.

(b) Witch hazel, NF XI.

3. Subpart D would be amended by adding new § 347.52, to read as follows:

§ 347.52 Labeling of astringent 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 an "astringent."

(b) *Indications.* The labeling of the product contains a statement under the heading "Indications" that is limited to the following:

(1) *For products containing aluminum acetate identified in § 347.12(a).* "For use as a wet dressing, compress, or soak for relief of inflammatory conditions and minor skin irritations due to allergies, insect bites, athlete's foot, poison ivy, or swelling associated with minor bruises and ulcerations of the skins."

(2) *For products containing witch hazel identified in § 347.12(b).* (i) "For use as an astringent for the treatment of bruises, contusions, and sprains."

(ii) "For protecting slight cuts and scrapes."

(iii) "For relieving muscular pains."

(iv) "For treating the pain and swelling of insect bites."

(v) "For use as an astringent for the treatment of skin irritation, sunburn, and external hemorrhoids."

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

(1) *For products containing aluminum acetate identified in § 347.12(a). (i)* "If condition worsens or symptons persist for more than 7 days, discontinue use of the product and consult a doctor."

(ii) "Do not cover wet dressing or compress with plastic to prevent evaporation."

(iii) "Keep away from eyes."

(iv) "For external use only."

(v) "Store in a cool dry place."

(2) *For products containing witch hazel identified in § 347.12(b).* For external use only."

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

(1) *For products containing aluminum acetate identified in § 347.12(a).* (i) Depending on the formulation and concentration of the marketed product, the manufacturer must provide adequate directions so that the resulting solution to be used by the consumer contains 2.5 to 5 percent aluminum acetate."

(ii) *For products containing aluminum acetate for use as a soak.* "Soak affected area for 15 to 30 minutes. Repeat 3 times a day. Discard remaining solution after use."

(iii) *For products containing aluminum acetate for use as a compress or wet dressing.* "Saturate a clean, soft, white cloth (such as a diaper or torn sheet) in the solution, gently squeeze, and apply loosely to the affected area. Saturate the cloth in the solution every 15 to 30 minutes and apply to the affected area. Repeat as often as necessary. Discard remaining solution after use.

(2) *For products containing witch hazel identified in § 347.12(b).* "Apply as often as necessary."

Interested persons may, on or before December 6, 1982, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before January 5, 1983. Received comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

Mark Novitch,

Acting Commissioner of Food and Drug.

Dated: August 27, 1982.

Richard S. Schweiker,

Secretary of Health and Human Services.

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