DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 347

[Docket No. 78N-021P]

RIN 0905-AA06

Skin Protectant Drug Products for Over-the-Counter Human Use; Proposed Rulemaking for Poison Ivy, Poison Oak, Poison Sumac, and Insect Bites Drug Products

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking amending the tentative final monograph (proposed rule) for over-the-counter (OTC) skin protectant drug products. The proposed rulemaking would establish conditions under which OTC skin protectant drug products for the treatment and/or prevention of poison ivy, poison oak, and poison sumac as well as for the treatment and/or neutralization of insect bites are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the statements on OTC drug products for poison ivy, poison oak, and poison sumac, and for use as insect bite neutralizers of the Advisory Review Panel on OTC Miscellaneous External Drug Products, public comments on an advance notice of proposed rulemaking that was based on those statements, and public comments on the notice of proposed rulemaking for OTC skin protectant drug products. (See the **Federal Register** of February 15, 1983; 48 FR 6820.) The agency's proposals concerning the use of other OTC drug products for treating the symptoms of poison ivy, poison oak, poison sumac, and insect bites are being published elsewhere in this issue of the **Federal Register**. These proposals are part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed rulemaking before the Commissioner of Food and Drugs by January 31, 1990. The agency is allowing a period of 120 days for comments and objections instead of the normal 60 days for the following reasons: (1) The concurrent publication of two rulemakings regarding OTC drug products for poison ivy, poison oak, poison sumac, and insect bites and (2) this document contains the first published evaluation of several submissions of data on OTC drug products for the treatment and/or prevention of these conditions that were made to, but not reviewed by, the Advisory Review Panel on OTC Miscellaneous External Drug Products (Miscellaneous External Panel). New data by October 3, 1990. Comments on the new data by December 3, 1990. Written comments on the agency's economic impact determination by January 31, 1990.

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

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

SUPPLEMENTARY INFORMATION: In the **Federal Register** of September 7, 1982, FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), advance notices of proposed rulemaking and reopened the administrative records for OTC external analgesic drug products (47 FR 39412) and skin protectant drug products (47 FR 39436). The notices were published to allow for consideration of statements on OTC drug products for the prevention of poison ivy, poison oak, poison sumac, and for use as insect bite neutralizers. The statements were prepared by the Miscellaneous External Panel, which was the advisory review panel responsible for evaluating data on the active ingredients used for these conditions. Interested persons were invited to submit comments by December 6, 1982. Reply comments in response to comments filed in the initial comment period could be submitted by January 5, 1983.

In the **Federal Register** of December 28, 1982 (47 FR 57738), in response to a request for an extension of time, the comment period and reply comment period for OTC skin protectant drug products were extended to February 4, 1983, and to March 7, 1983, respectively.

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

One trade association and five drug manufacturers submitted comments concerning the use of skin protectant drug products for poison ivy, poison oak, poison sumac, and insect bites (poison ivy-oak-sumac and insect bites). Some of these comments were submitted to both the external analgesic and skin protectant rulemakings. In those cases where the same comments were submitted to both rulemakings, the comments will be addressed only in the appropriate amendment to either the proposed rule for OTC skin protectant drug products or for OTC external analgesic drug products published elsewhere in this issue of the **Federal Register**. Copies of the comments received are on public display in the Dockets Management Branch.

The Panel provided general statements on OTC drug products for the prevention of poison ivy, poison oak, poison sumac, and for use as insect bite neutralizers. However, the Panel did not review all of the submitted individual ingredients nor develop labeling for drug products for these indications. Also, the Panel reviewed only ingredients with labeling claims for prevention of poison ivy, poison oak, or poison sumac, or for treatment of insect bites by neutralization or inactivation of insect venom. However, many submissions to the Panel were for drug products used to treat the symptoms (i.e., itching, minor irritations) of poison ivy-oak-sumac and insect bites by the mechanism of providing a physical or mechanical barrier to protect the exposed skin surfaces from harmful or annoying stimuli. Additionally, a number of skin protectant drug products labeled for the treatment and/or prevention of poison ivy, poison oak, poison sumac and for the treatment and/or neutralization of insect bites were not submitted to the Miscellaneous External Panel. Therefore, the agency is expanding the scope of this segment of the skin protectant rulemaking to include all OTC skin protectant drug products labeled for any of these uses.

In this document, the agency is addressing comments concerning drug products for the treatment and/or prevention of poison ivy, poison oak, and poison sumac and for the treatment and/or neutralization of insect bites when the mechanism of action for these uses involves the ingredient's ability to neutralize or inactivate insect venom or the ingredient's ability to provide a mechanical barrier to protect exposed skin surfaces from harmful or annoying stimuli. In the external analgesic rulemaking (published elsewhere in this issue of the **Federal Register**), the agency is addressing claims for the treatment of symptoms of poison ivy-oak-sumac and insect bites when the mechanism of action for these claims involves the depression or stimulation of cutaneous sensory receptors.

In the **Federal Register** of February 15, 1983 (48 FR 6820), the agency published a tentative final monograph (proposed rule) for OTC skin protectant drug products. The agency issued this notice after considering the report and recommendations of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products (Topical Analgesic Panel) and public comments on an advance notice of proposed rulemaking that was based on those recommendations.

Interested persons were invited to submit comments by April 18, 1983, new data by February 15, 1984, and comments on new data by April 16, 1984. In response to that notice, one manufacturer's association and five drug manufacturers submitted comments concerning the use of skin protectant ingredients for the treatment and/or prevention of poison ivy, poison oak, and poison sumac as well as for the treatment and/or neutralization of insect bites. The agency is also addressing these comments in this notice of proposed rulemaking. Copies of the comments received are on public display in the Dockets Management Branch (address above).

In this notice of proposed rulemaking, FDA responds to public comment and further discusses its position on OTC skin protectant drug products for the treatment and/or prevention of poison ivy, poison oak, and poison sumac as well as for the treatment and/or neutralization of insect bites. Final agency action on this matter will occur with the publication at a future date of a final rule relating to OTC skin protectant drug products for these conditions.

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

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

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

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

I. The Agency's Tentative Conclusions on the Comments

The agency has reviewed the comments submitted to this rulemaking. As noted above, most of the comments were also submitted to the external analgesic rulemaking. The agency has addressed the general comments in the proposed rulemaking to amend the tentative final monograph for OTC external analgesic drug products, published elsewhere in this issue of the **Federal Register**. These comments are incorporated into this rulemaking.

1. One comment requested that colloidal oatmeal be included in the skin protectant monograph as a safe and effective ingredient for the claim: "For prompt temporary relief of itchy, sore, sensitive skin due to: * * * poison ivy/oak * * *." The comment based its request on the Miscellaneous External Panel's review of colloidal oatmeal as an antipruritic at that Panel's 23d meeting on January 29 and 30, 1978. The comment noted that the Panel found colloidal oatmeal at all concentrations to be safe and effective as a bath additive, cleansing bar, and soak for the symptomatic relief and treatment of dry skin and the resultant itching (Ref. 1).

The comment contended that colloidal oatmeal falls within the Topical Analgesic Panel's definition of a skin protectant. The comment argued that, due to its physical and chemical properties, colloidal oatmeal isolates exposed skin or mucous membrane surface from harmful or annoying stimuli. (See proposed § 347.3 at 43 FR 34628 at 34648; August 4, 1978.) Moreover, the comment added that colloidal oatmeal meets the Panel's criteria described at 43 FR 34630 in that it protects by mechanical or other physical means, is inert, insoluble, finely subdivided, and adsorbs some moisture. The comment stated that colloidal oatmeal that is dispersed in water and applied to the skin deposits particles on the skin and leaves behind an occlusive film barrier that is helpful in protecting skin against irritation and in soothing irritated or pruritic skin conditions. The comment added that colloidal oatmeal when added to water controls the osmotic pressure of water with respect to the skin and permits adequate water to enter into the stratum corneum. The comment stated that the oatmeal leaves behind a thin occlusive film on the skin and this serves to hold in the adsorbed moisture. The result of this coating is that the skin is protected against irritation; hence, the ingredient has an antipruritic and generally soothing effect. The comment noted that the Topical Analgesic Panel stated at 43 FR 34630 that "* * * the fluids from seeping rashes or toxic dermatoses (poison ivy, poison sumac, * * *) are absorbed or adsorbed by many of these drugs. Often itching is ameliorated." Based on the above, the comment contended that the following claim for colloidal oatmeal is justified: "For prompt temporary relief of itchy, sore, sensitive skin due to: * * * poison ivy and oak * * *."

The Topical Analgesic Panel stated at 43 FR 34630 that well-controlled clinical

studies have not been conducted for most of the skin protectant ingredients. The Panel recommended that the requirement for well-controlled studies be waived, on the grounds that clinical studies are not necessary to support the use of mechanical barriers such as these ingredients to protect the skin from further injury. The agency agrees with this recommendation regarding skin protectant (physical barrier type) ingredients.

In addition, the agency agrees that colloidal oatmeal qualifies as a skin protectant because of its barrier-like properties. Montebovi (Ref. 2) identified and evaluated a number of hydrophilic colloids including colloidal oatmeal using the "Gold Number" as a means of determining the protective ability of hydrophilic solutions. The "Gold Number" is an in vitro physical chemical determination intended to measure the protective ability of hydrophilic colloids. Montebovi also measured and evaluated the viscosity of hydrophilic colloids with particular reference to colloidal oatmeal and stated that:

> The colloidal adsorbents are used in dermatology primarily for their protective demulcent effects. On the basis of the physical properties of the agents commonly used for this purpose, the role of colloidal oatmeal appears to be well founded. Chemically it is made up of gums, protein, and oil in a ratio which is consistent with the desirable characteristics of the purified agents. Its high protective colloidal activity is demonstrated by the low Gold Number. The viscosity and surface tension establish a good spreading and clinging property which would be necessary for sustained protective action.

Furthermore, the agency has reviewed the data submitted by the comment (Ref. 3) in view of the Panel's recommendations and concludes there is sufficient information to demonstrate that colloidal oatmeal is safe and effective when used in a bath to relieve minor skin irritation and itching due to poison ivy, poison oak, and poison sumac. The comment cited the Merck Manual (Ref. 4) which recommends that, in extensive pruritis, the patient should soak for 10 to 20 minutes twice a day in a colloidal oatmeal bath. Also, the American Medical Association Drug Evaluations (Ref. 5) states that pruritus accompanying acute dermatitis or extensive exanthematous lesions is often alleviated by immersion of the part or the entire body in water and that colloidal substances can be added to such baths for their soothing and antipruritic activities. It recommends the use of colloidal oatmeal added to a tub half-filled with water.

Other references submitted by the comment also describe the use of colloidal oatmeal in therapeutic baths to relieve minor skin irritation. Epstein (Ref. 6) recommended tepid colloidal oatmeal baths (250 grams in a tub of water twice daily) to ease discomfort in cases of generalized dermatitis. Lewis and Wheeler (Ref. 7) recommended the use of baths (e.g., colloidal oatmeal ½ to 1 cupful to a tub of water) when dermatosis is extensive and stated that such baths are used for their soothing or antipruritic properties and are often the most efficient method for applying medication to exudative surfaces. Whyte (Ref. 8) stated that, in acute (exudative) dermatitis and subacute dermatitis (less exudative), colloidal oatmeal in warm water should be used to soothe and coat the inflamed skin with a bland colloid. Whyte added that a paroxysm of itching is often best treated by a comfortable warm colloid bath once or more daily. O'Brasky (Ref. 9) described one patient with "an erythematous, vesicular and edematous eruption, typical of a contact dermatitis (ivy) * * * ." The investigator stated that the patient responded well to treatment with colloidal oatmeal baths (no other medication was used), and was discharged 10 days after treatment began. O'Brasky treated 111 patients with dry skin manifestations (including one patient with multiple insect bites) and noted that the colloidal oatmeal baths had antipruritic properties because patients complained of recurrent itching when the baths were omitted.

The agency agrees with the comment that the evidence is supportive of the general recognition of colloidal oatmeal as a safe and effective skin protectant. Based on the available information, the agency believes that colloidal oatmeal could be classified as a Category I skin protectant when labeled with the following claim: "Provides temporary skin protection and relieves minor irritation and itching due to poison ivy, poison oak, poison sumac, and insect bites."

However, in order for colloidal oatmeal to be generally recognized as safe and effective as a skin protectant, the agency must have sufficient data on the composition and concentration of the different constituents and the quantity (range) of each that is contained in marketed products. For an ingredient or mixture to be included in an OTC drug final monograph, it is necessary to have publicly available chemical information that can be used by all manufacturers to determine that the ingredient is appropriate for use in their products.

The comment submitted a report by MonteBovi (Ref. 2) that describes colloidal oatmeal as a specifically milled constant fraction of the colloid-producing portion of the oat grain, having a chemical analysis of 46 percent carbohydrate, 9.0 percent oil, 24.0 percent protein, 8.0 percent moisture, and 0.03 percent crude fiber. However, the agency does not find this information to be an adequate public standard for colloidal oatmeal.

The agency believes that it would be appropriate for interested parties to develop with the United States Pharmacopeial Convention appropriate standards for the quality and purity of colloidal oatmeal. In this tentative final monograph, colloidal oatmeal is proposed in Category I. However, should interested parties fail to provide necessary information so that an appropriate standard may be established, colloidal oatmeal will not be included in a final monograph.

The comment submitted the following directions for the use of colloidal oatmeal in a bath: Turn the warm bath water on to full force, then slowly sprinkle one cupful of colloidal oatmeal into the bathtub under the faucet. Before entering the tub, stir any colloidal oatmeal that may have settled to the bottom of the tub. Bathe for 15 to 20 minutes. For infants, use 2 tablespoonfuls per bath. Use once or twice daily, or as directed by your physician.

The agency is proposing these directions for colloidal oatmeal with minor revisions. Because it is desirable to leave a thin layer of the colloidal oatmeal on the skin after bathing, the agency is adding directions to pat the skin dry, rather than to rub it dry, after the bath. In addition, the submitted labeling recommends a dosage for infants, but it does not specify a particular age range, how much water to which the 2 tablespoonfuls of colloidal oatmeal should be added, or how it should be added to ensure dispersion of the colloidal oatmeal to make a colloidal suspension. In general, infants would be bathed in something smaller than an adult-sized tub and the amount of water would be less. Therefore, the agency has not included specific directions for children under 2 years of age at this time and requests specific comment on appropriate directions for this age group as well as a possible lower age limit for use of this ingredient.

Based on the submitted labeling, the following directions are being proposed for colloidal oatmeal for use as a skin protectant: Adults and children 2 years of age and over: For use as a soak in a

tub. Turn tub warm water faucet on to full force, then slowly sprinkle 1 cupful of colloidal oatmeal directly under the faucet into the tub. Before entering the tub, stir any colloidal oatmeal that may have settled to the bottom of the tub. Soak the affected area for 15 to 20 minutes as needed. Do not rub area dry, but instead pat dry so that a thin layer of the colloidal oatmeal will be left on the skin. Soak once or twice daily, or as directed by your doctor. Children under 2 years of age: consult a doctor.

In addition, several references mentioned that patients should be careful when using colloidal oatmeal in a bath to avoid slipping in the tub (Ref. 3). Current labeling for the submitted product states: "Take special care to avoid slipping" (Ref. 10). The agency believes it is appropriate to propose that a statement like this be required as a warning for skin protectant drug products containing colloidal oatmeal. The agency is expanding the statement to read "Take special care to avoid slipping when getting into and out of the tub" to make it more specific for consumers.

References

(1) Summary of Minutes of the Twenty-Third Meeting of the Advisory Review Panel on OTC Miscellaneous External Drug Products, January 29 and 30, 1978, OTC Volume 16DPA1, Docket No. 78N–0021, Dockets Management Branch.

(2) MonteBovi, A. J., "The Colloidal Demulcents. I. Physical and Chemical Properties," *American Journal of Pharmacy*, 126:4–7, 1954.

(3) OTC Volumes 160069 and 160070.

(4) "The Merck Manual," 12th Ed., Merck Sharpe & Dohme Research Laboratories, West Point, PA, p. 1431, 1972.

(5) "Drug Evaluations," 6th Ed., American Medical Association, Chicago, p. 1030, 1986.

(6) Epstein, W. L., "Contact Dermatitis," in OTC Volume 160070.

(7) Lewis, G. M., and C. E. Wheeler, Jr., "Practical Dermatology," in OTC Volume 160070.

(8) Whyte, H. J., "Atopic Dermatitis," in OTC Volume 160070.

(9) O'Brasky, L., "Management of Extensive Dry Skin Conditions," *Connecticut Medicine*, 23:20, 1959.

(10) Labeling for Colloidal Oatmeal Product in OTC Volume 06P1STFM, Docket No. 78N–021P, Dockets Management Branch.

2. Two comments requested that corn starch be classified as a Category I skin protectant for the treatment of poison ivy, poison oak, and poison sumac. One comment, noting that the agency had tentatively deleted corn starch from the skin protectant tentative final monograph until diaper rash drug products are reviewed, stated that although corn starch is widely used in diaper rash products, it is also an ingredient in skin protectant products for use by the general population. The second comment agreed with the agency's proposal that the maximum Category I concentration of corn starch be raised from 85 to 97 percent (48 FR 6820 at 6826). However, the comment disagreed with the agency's statement in the tentative final monograph that "at the present time none of the proposed Category I indications are applicable to corn starch," (48 FR 6820 at 6828). Accordingly, both comments requested that corn starch be included in the skin protectant monograph as a general skin protectant labeled with the following indication proposed in § 347.50(b)(3) of the tentative final monograph: "Dries the oozing and weeping of poison ivy, poison oak, and poison sumac."

The Topical Analgesic Panel classified 10 to 85 percent corn starch as a Category I skin protectant in its report (43 FR 34628 at 34636). One of the skin protectant indications recommended by the Panel for corn starch in § 347.50(b) reads "For symptoms of oozing or weeping" (optional, any or all of the following) "due to contact dermatitis, poison oak, or poison ivy" (43 FR 34648). In its discussion of corn starch, the Panel mentioned that absorption by corn starch probably surpasses that of any powder described in the official compendia. It protects the skin by absorbing moisture, perspiration, and noxious secretions, and it soothes dermal irritation and itching (43 FR 34636). However, the Panel did not cite any studies or literature references on the use of corn starch for the treatment of poison ivy, poison oak, poison sumac, or other types of contact dermatitis.

In the tentative final monograph for OTC skin protectant drug products (48 FR 6820 at 6828), the agency stated that "at the present time, none of the proposed Category I indications are applicable to corn starch. Most of the uses of corn starch discussed by the Topical Analgesic Panel are cosmetic uses. The primary OTC drug use of corn starch appears to be in diaper rash drug products." Therefore, the agency did not include corn starch in the tentative final monograph, but deferred evaluation of corn starch until its use in diaper rash drug products was reviewed. That evaluation will be published in a future issue of the **Federal Register**.

In the present document, the agency is classifying topical starch in Category III for the treatment of poison ivy, poison oak, and poison sumac.

Note: Although "corn starch" has been used as the name for this ingredient, "topical starch" is the official title used in the United States Pharmacopeia XXI (Ref. 1).

The comments did not submit any data on the use of topical starch for use as a treatment for poison ivy, poison oak, and poison sumac. In addition, the submissions to the Panel do not contain any data on the use of topical starch as a poison ivy treatment. Several articles in one submission state that starch is used to cover and protect the skin, mucous membranes, ulcers, and wounds, but also state that water-absorbent powders should not be used on extensive profusely secreting raw surfaces, as they tend to cake and form adherent crusts, and that starch becomes doughy (Refs. 2 through 5). Further, although two submissions to the Panel contain information on products containing topical starch and include poison ivy labeling claims (e.g., helps dry weeping of poison ivy, poison oak, and poison sumac), the therapeutic properties of the products were attributed to other ingredients in the product, and topical starch was only included as an inactive ingredient (Ref. 6). Other submissions of products containing topical starch did not contain any poison ivy treatment labeling claims (Ref. 7). Additionally, the agency is unaware of any products that bear poison ivy treatment labeling claims that contain topical starch as an active ingredient.

The initial symptoms following exposure to poison ivy include erythema or rash. The development of raised lesions follows, and finally vesicles and bullae form, caused by fluid accumulation in the epidermis. The initial lesions usually are marked by mild to intense itching and burning. The affected area, often hot and swollen, oozes and eventually dries and crusts. Most cases of poison ivy are self-limiting and disappear in 14 to 20 days (Ref. 8). Topical starch is safe when applied topically, but should not be used on broken skin because crusting and skin granulomas have been known to occur when starch is applied to broken skin (Refs. 9 and 10). Thus, because of the weeping and oozing vesicles associated with poison ivy and related contact dermatitis, the agency believes that topical starch may not be appropriate to treat the symptoms of poison ivy, poison oak, and poison sumac. Further, because of a lack of data on effectiveness and a suitable concentration of topical starch for this use, and because the agency is unaware of any marketed products that contain topical starch as an active ingredient for the treatment of poison ivy, as discussed above, the agency proposes that topical starch be classified in Category III as a skin protectant drug

product for the treatment of poison ivy, poison oak, and poison sumac. Other skin protectant uses of topical starch will be addressed in the diaper rash amendment to the tentative final monograph for OTC skin protectant drug products and in the final monograph for OTC skin protectant drug products.

References

(1) "The United States Pharmacopeia, XXI—The National Formulary XVI," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 984, 1985.

(2) Welsh, A.L., "Powders," *in* "The Dermatologist's Handbook," Charles C. Thomas, Springfield, IL, pp. 12–14, 1957.

(3) Martin, E.W., "Techniques of Medication. A Manual on the Administration of Drug Products," J.B. Lippincott Co., Philadelphia, pp. 56–57, 1969.

(4) Balsam, M.S., and E. Sagarin, editors, "Cosmetics: Science and Technology," Vol. 1, 2d Ed., Wiley-Interscience, New York, pp. 136–138 and 152–154, 1972.

(5) Swinyard, E.A., "Locally Acting Drugs," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., edited by L. S. Goodman and A. Gilman, The Macmillan Co., New York, p. 989, 1970.

(6) OTC Volumes 160040 and 160077.

(7) OTC Volumes 060137 and 160242.

(8) Wormser, H., "Poison Ivy and Poison Oak Products," *in* "Handbook of Nonprescription Drugs," 8th Ed., American Pharmaceutical Association, Washington, pp. 633–642, 1986.

(9) Kelly, R., and P.E. Campbell, "Granuloma Glutaeale Infantum with Starch Granules in the Lesion," *The Medical Journal of Australia*, 2:438–439, 1973.

(10) Leonard, D.D., "Starch Granulomas," *Archives of Dermatology*, 107:101–103, 1973.

3. One comment requested that sodium bicarbonate (baking soda) be classified as a Category I skin protectant for drying the oozing and weeping of poison ivy, poison oak, and poison sumac, and for protecting and relieving the irritation associated with various skin problems, such as poison ivy and minor insect bites and stings. Referring to the tentative final monograph for OTC skin protectant drug products (48 FR 6820 at 6830), which discussed FDA's decision to transfer sodium bicarbonate from the rulemaking for OTC skin protectant drug products to the rulemaking for OTC external analgesic drug products, the comment stated that baking soda should be considered in both rulemakings. The comment expressed concern that sodium bicarbonate had been placed in Category II as an insect bite neutralizer by the Miscellaneous External Panel in its statement on OTC insect bite neutralizer drug products, published in the **Federal Register** of September 7, 1982 (47 FR 39448). The comment contended that the ingredient was incorrectly categorized. The comment asked that the data on sodium bicarbonate previously submitted to the Miscellaneous External Panel (Ref. 1) and to the rulemakings for OTC skin protectant and external analgesic drug products (Refs. 2 through 5) be reconsidered as demonstrating that sodium bicarbonate has been used and marketed for many dermatological conditions, including for the relief, protection, and for drying the oozing and weeping of poison ivy, poison oak, and poison sumac, and for the relief of itching of poison ivy-oak-sumac and insect bites. The comment added that a survey (Ref. 1) indicates that many dermatologists and other physicians routinely prescribe sodium bicarbonate for a wide variety of external drug uses, including, but not limited to, relief of minor insect stings and bites.

The comment noted that, although sodium bicarbonate has not been the subject of double-blind clinical trials (a concept of relatively recent development, circa 1952), it has been used for a long time for its effectiveness in the treatment of a variety of skin conditions (Ref. 6). The comment included a "dermatological summary of baking soda" (sodium bicarbonate) (Ref. 6) which contained references in the medical literature on the topical use of sodium bicarbonate (e.g., as a powder and in a bath) in a number of dermatological conditions.

The Topical Analgesic Panel classified sodium bicarbonate as safe and effective for use as a skin protectant (43 FR 34628 at 34640). That Panel concluded that sodium bicarbonate is safe for use as a skin protectant with no age or concentration limits. That Panel stated that sodium bicarbonate has a long history of market acceptability, soothes irritated skin, and as a topical protectant is effective in the symptomatic relief of minor irritations, insect bites, and stings (43 FR 34640). That Panel stated that sodium bicarbonate is effective as a skin protectant due to its absorbent properties, but did not include the ingredient in its table which categorized the purposes (i.e., for dryness, wetness, or lubricity) for which Category I skin protectants are used (43 FR 34632).

In the tentative final monograph for OTC skin protectant drug products (48 FR 6820 at 6830), the agency stated that the Panel pointed out that sodium bicarbonate is an effective antipruritic in relieving itching due to nonpoisonous insect stings and bites, or due to sunburn, and that it is also used to relieve the pain of minor acid burns. Because the indication "for the temporary relief of pain and itching due to minor burns, sunburn, * * * insect bites, and minor skin irritations" was being addressed in the external analgesic rulemaking (December 4, 1979; 44 FR 69768), the agency transferred sodium bicarbonate to that rulemaking proceeding.

Now that all of the information submitted on the uses of sodium bicarbonate has been reviewed, the agency has determined that sodium bicarbonate should be addressed in the skin protectant rulemaking, not in the external analgesic rulemaking. For reasons discussed below, the agency believes that claims related to the "relief of itching of poison ivy and insect bite" for sodium bicarbonate should be considered under the skin protectant rulemaking.

The agency has reviewed the data referred to by the comment (Refs. 1 through 6), which include information on (1) the historical use of sodium bicarbonate as a paste for treatment of skin irritation, including insect bites and poison ivy, (2) eye, skin, and oral toxicity data, which indicate that sodium bicarbonate is relatively nontoxic, (3) a survey of dermatologists and general practitioners in which it was concluded that one out of three responding dermatologists and one out of two responding general practitioners have used or recommended use of sodium bicarbonate for relief of insect bites, minor burns, and pruritis, and (4) efficacy data consisting of references indicating that sodium bicarbonate used as a paste, wet dressing, or in a tub bath provides relief of skin irritation and minor skin conditions such as mild itching, erythema, and insect bites, and because of its emollient effect relieves skin irritation.

The data show that alkaline baths (sodium bicarbonate) are useful in chronic, scaly dermatoses and urticaria, and help to soften the skin. However, for insect bites and stings, first aid measures are not entirely effective because the bite wound extends beneath the skin, although a paste made of baking soda and cold cream provides some relief. The comment claimed that sodium bicarbonate reduces pain by neutralizing the formic acid injected by the insect.

The agency agrees with the Topical Analgesic Panel that sodium bicarbonate can be generally recognized as a safe and effective skin protectant (43 FR 34628 at 34640). Additionally, the agency agrees with the Panel's statement in its report on skin protectant drug products that sodium bicarbonate has antipruritic activity (43 FR 34640). Moreover, other information discussed above indicates that sodium bicarbonate

provides relief of itching (Refs. 1 through 6). The Panel's discussion of sodium bicarbonate's antipruritic activity concerned the ingredient's use as a skin protectant, not as an external analgesic. The relief of itching attributed to skin protectants was based on the pharmacologic action of these drugs in providing a physical or mechanical barrier to protect exposed skin surfaces from harmful or annoying stimuli (43 FR 34630). The pharmacological action of external analgesics is to depress or stimulate the cutaneous sensory receptors as a means of relieving the symptoms of pain and itching (44 FR 69768 at 69772). Thus, sodium bicarbonate's mechanism of action in relieving itching is based on its use as a mechanical barrier (i.e., skin protectant), rather than on physiological or physiochemical factors (i.e., external analgesic). Therefore, the "relief of itching" claim for sodium bicarbonate is addressed in this rulemaking.

Based on the available information, the agency believes that sodium bicarbonate can be classified as a Category I skin protectant when labeled with the following claim: "Provides temporary skin protection and relieves minor irritation and itching due to poison ivy, poison oak, poison sumac, and insect bites." However, the submitted data do not provide any information on sodium bicarbonate's drying effect in conditions such as poison ivy, poison oak, and poison sumac; therefore, the indication "Dries the oozing and weeping of poison ivy, poison oak, and poison sumac" is not being proposed for sodium bicarbonate. Nor is there evidence to support the use of sodium bicarbonate as an insect bite neutralizer. Therefore, the agency is retaining the Category II classification that was proposed for this ingredient as an insect bite neutralizer by the Miscellaneous External Panel (47 FR 39436 at 39448).

The Topical Analgesic Panel did not recommend any age or concentration limits for the use of sodium bicarbonate. The agency is not proposing any concentration limits for sodium bicarbonate in this amendment; however, it is including an age limitation. No data were provided on the use of sodium bicarbonate on infants for the requested uses. The agency is aware of one report of an adverse reaction in a 4-month-old infant after treatment of diaper rash with sodium bicarbonate (Ref. 7). The adverse reaction report states that liberal amounts of sodium bicarbonate and petrolatum had been applied to a severe diaper rash at every diaper change for more than a week. The infant experienced hypokalemic metabolic alkalosis which the authors attributed to excessive sodium bicarbonate absorption from the baking soda that was applied to the diaper rash. The authors postulated that metabolic alkalosis occurred because the infant's immature renal system was not able to effectively excrete the excessive load of bicarbonate.

The agency notes that a marketed product containing sodium bicarbonate provides directions for emollient baths to relieve skin irritations (Ref. 1). Regarding the use of sodium bicarbonate for such baths, the submission (Ref. 1) cites the Merck Manual (Ref. 8) as recommending that 8 ounces of sodium bicarbonate be dissolved in about 30 gallons of warm water and that the patient should remain in the bath for 10 to 30 minutes or longer. The skin should be patted dry rather than rubbed so that a thin film of the drug remains on the skin. Other submitted data (Ref. 6) indicated that although there is variation regarding the recommended or optimal concentration of sodium bicarbonate for baths and solutions, a range of 1 to 5 percent would encompass most of the concentrations.

The following directions are being proposed for sodium bicarbonate for use as a skin protectant: "Adults and children 2 years of age and over: Topical dosage is 1 to 100 percent sodium bicarbonate.

(i) *For use as a paste.* Add sufficient water to the sodium bicarbonate to form a paste and apply to the affected area of the skin as needed. Children under 2 years of age: Consult a doctor.

(ii) *For use as a soak in a tub.* Dissolve 1 to 2 cupfuls of this product in a tub of warm water and soak for 10 to 30 minutes as needed. Do not rub dry, but instead pat dry so that a thin layer of the sodium bicarbonate will be left on the skin. Children under 2 years of age: Consult a doctor.

(iii) *For use as a wet dressing.* Add sodium bicarbonate to water to make a solution. Use a container in which you can saturate a cloth. 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."

The agency has considered the warnings proposed for skin protectants in § 347.50(c) to determine which are applicable to sodium bicarbonate. In the tentative final monograph for OTC skin protectant drug products (48 FR 6820 at 6830), a comment requested that sodium bicarbonate be exempted from the general warning for skin protectants "For external use only" because it is both a food and an antacid and, thus, this warning would confuse consumers. The agency agrees that sodium bicarbonate can be exempted from the warning "For external use only." Further, the directions for using the ingredient as a skin protectant clearly indicate that the product is for external use. The comment also requested that sodium bicarbonate be exempted from the warning "Avoid contact with the eyes." The comment contended that the drug is nonirritating according to the Draize rabbit eye irritation test, and it is used in swimming pools and baths.

The agency has reviewed the eye irritation study referred to by the comment (Ref. 1). Six rabbits were tested using sodium bicarbonate (0.086 grams) instilled into the right eye. All rabbits exhibited redness of the conjunctiva because of sodium bicarbonate, and two exhibited a slight discharge. However, as stated by the comment, the drug would not be considered an eye irritant according to the standards prescribed in the Draize testing methodology. Although sodium bicarbonate is not considered an eye irritant, it caused redness of the eye in rabbits. Because any product that might be used on the face could accidentally get into the eye and cause irritation, the agency believes that a general warning to avoid contact with the eyes is appropriate. Therefore, the warning is being retained for sodium bicarbonate. Thus, the following warnings proposed in § 347.50(c) (1) and (2) are applicable to sodium bicarbonate: (1) "Avoid contact with the eyes," and (2) "If condition worsens or does not improve within 7 days, consult a doctor."

The use of sodium bicarbonate for other skin protectant uses will be discussed in future issues of the **Federal Register**.

References

(1) OTC Volume 160032.

(2) Comment C00027, Docket No. 78N–0021, Dockets Management Branch.

(3) Comment C00050, Docket No. 78N–0021, Dockets Management Branch.

(4) Comment C00047, Docket No. 78N–0301, Dockets Management Branch.

(5) Comment C00085, Docket No. 78N–0301, Dockets Management Branch.

(6) Eisenstat, B.A., "Dermatological Summary of Baking Soda," unpublished study, pp. 1–7, October 7, 1983, in OTC Volume 06PISTFM, Docket No. 78N–021P, Dockets Management Branch.

(7) Gonzalez, J., and R.J. Hogg, "Metabolic Alkalosis Secondary to Baking Soda

Treatment of a Diaper Rash," *Pediatrics*, 67:820–822, 1981.

(8) Lyght, C.E., editor, "The Merck Manual," 9th Ed., Merck & Co., Rahway, NJ, p. 1756, 1956.

4. Two comments contended that limiting the statement of identity for different skin protectant drug products to the one term "skin protectant" is too restrictive, that other equally descriptive terms are appropriate, and that other statements of identity should be allowed for such products. One comment stated that the statement of identity should reflect the mode of action and suggested that the term "poison ivy and oak (dosage form)" be allowed for skin protectant drug products labeled for this use. The other comment argued that because the tentative final monograph provides separate and distinct indications for each group of skin protectant drug products, there should be equally separate and distinct statements of identity for each group. According to the comment, the large diversity of appropriate indications justifies an equally diverse list of appropriate statements of identity that would properly inform the consumer of the intended use of the product. The comment requested that additional statements of identity be included in the skin protectant monograph and suggested such statements as "poison ivy, oak, sumac treatment," "poison ivy, oak, sumac protectant," and "drying (dosage form)" for ingredients proposed in § 347.50(b)(3) and also for corn starch.

The agency agrees with one comment that the term "poison ivy, oak, sumac treatment" is an appropriate statement of identity for skin protectant drug products used for this purpose, including the ingredients colloidal oatmeal and sodium bicarbonate that are proposed for Category I status in this document (see comments 1 and 3 above.). However, the agency does not find the statements "poison ivy and oak (dosage form)" and "poison ivy, oak, sumac protectant" to be as descriptive and informative to consumers. Further, the agency believes that the word "protectant" in the latter statement is confusing and could be interpreted as protecting against poison ivy, oak, and sumac.

In addition, the agency believes that while the statement "drying (dosage form)" describes the principal intended action of skin protectant drug products used for the proposed indication ("Dries the oozing and weeping of poison ivy, poison oak, and poison sumac"), it is too general if used alone. If the concept of "drying" is combined with "poison ivy, oak, and sumac," it would be an acceptable statement of identity. However, this statement of identity is not appropriate for the ingredients colloidal oatmeal and sodium bicarbonate, because the agency is not proposing that these ingredients be Category I for the indication "Dries the oozing and weeping of poison ivy, poison oak, and poison sumac." (See comments 1 and 3 above.) Accordingly, the agency is proposing that the statement of identity in § 347.50(a) for skin protectant drug products used to treat poison ivy, poison oak, and poison sumac be revised to read as follows: "(a) *Statement of Identity.* The labeling of the product contains the established names of the product, if any, and identifies the product with one or more of the following:

(1) "Skin protectant."

(2) *For products containing any ingredient in § 347.10 (b), (c), (g), (k), (l), or (m).* "Poison ivy, oak, sumac drying" (insert dosage form, e.g., "cream," "lotion," or "ointment").

(3) *For products containing any ingredient in § 347.10 (b), (c), (g), (k), (l), (m), (t), or (u).* "Poison ivy, oak, sumac treatment.

II. The Agency's Evaluation of the Submissions

The Miscellaneous External Panel discussed only the use of OTC drug products for the prevention of poison ivy, poison oak, and poison sumac and for use as insect bite neutralizers. The Panel recommended that the agency consider in appropriate rulemakings ingredients and labeling claims submitted for treating poison ivy, poison oak, poison sumac, and their related symptoms (47 FR 39436 at 39441).

In this document, the agency discusses the use of OTC skin protectant drug products for the treatment and/or prevention of poison ivy, poison oak, and poison sumac as well as for the treatment and/or neutralization of insect bites. The agency has evaluated a number of submissions (Ref. 1) that were not reviewed by the Panel. Some of the submissions include drug products that are no longer marketed or that have been reformulated to include active ingredients and/or conditions that were proposed in the tentative final monograph for OTC skin protectant drug products (48 FR 6820). The manufacturers of these drug products have requested that their submissions or portions of their submissions concerning these drug products be withdrawn from further consideration in this rulemaking, as follows:

1. Submissions (Ref. 2) concerning drug products containing stabilized aloe vera for topical use for numerous indications including the symptoms of insect bites and poison ivy were withdrawn by the manufacturers (Refs. and 4).

2. Submissions and portions of submissions (Ref. 5) concerning drug products containing zirconium oxide for the prevention and/or treatment of poison ivy, poison oak, and poison sumac were withdrawn by the manufacturers (Refs. 6 and 7).

References

(1) OTC Volumes 160032, 160074, 160152, and 160186.

(2) OTC Volumes 160143, 160196, 160252, 160261, 160273, and 160274.

(3) Letter from J.F. Girardi, Aloe Creme Laboratories, to W.E. Gilbertson, FDA, dated October 22, 1988, included in OTC Volume 06PISTFM, Docket No. 78N–021P, Dockets Management Branch.

(4) Letters from A. Davis, Aloe Vera of America, to W.E. Gilbertson, FDA, dated October 24, 1986 and May 20, 1988, included in OTC Volume 06PISTFM, Docket No. 78N–021P, Dockets Management Branch.

(5) OTC Volumes 160030, 160076, and 1600288.

(6) Letter from J. Wright, North Health Care, to W.E. Gilbertson, FDA, dated April 15, 1988, included in OTC Volume 06PISTFM, Docket No. 78N–021P, Dockets Management Branch.

(7) Letter from R. Kirpitch, Warner-Lambert, to A. Mustafa, FDA, dated May 10, 1988, included in OTC Volume 06PISTFM, Docket No. 78N–021P, Dockets Management Branch.

5. One manufacturer submitted information to the Miscellaneous External Panel requesting Category I status for a drug product containing 6 percent ferric chloride solution labeled as an astringent "for topical use only in prevention of ivy poisoning" and as a "preventative solution for poison ivy, poison oak, poison sumac" (Refs. 1, 2, and 3).

The Miscellaneous External Panel reviewed these submissions, but inadvertently did not cite one of them (Ref. 1) in its statement on OTC drug products for the prevention of poison ivy, oak, and sumac (47 FR 39412 at 39417 and 39441). The agency has reviewed these submissions and determined that the volume not cited by the Panel contains only labeling for the manufacturer's products and that one of the submissions that the Panel did review and cite (Ref. 2) contains all of the supporting information for the ferric chloride product.

The Panel stated that the submissions contained no substantial data to establish the safety and effectiveness of ferric chloride to prevent poison ivy, poison oak, or poison sumac and classified this ingredient in Category II

(47 FR 39412 at 39417 and 39436 at 39441). No additional data have been submitted. The agency concurs with the Panel's determination that the manufacturer's submissions do not contain substantial data in support of the safety or effectiveness of ferric chloride and with the Panel's recommendation that ferric chloride be classified Category II for the prevention of poison ivy, poison oak, or poison sumac.

References

(1) OTC Volume 160074.
(2) OTC Volume 160152.
(3) OTC Volume 160132.

6. One submission (Ref. 1) contained a label for a spray product containing benzalkonium chloride and polyvinylpyrrolidone-vinyl acetate copolymers as active ingredients claimed to be effective for the treatment of itching and burning of poison ivy, poison oak, and poison sumac and "in reducing the swelling and itching of insect bites, from chiggers, mosquitoes, bees, wasps, etc."

The submission did not contain any data to support the claims made for these ingredients. Because no information has been submitted to the agency on the safety and effectiveness of polyvinylpyrrolidone-vinyl acetate copolymers, the agency is classifying this ingredient in Category II in this rulemaking. The agency proposed a Category III classification for benzalkonium chloride as a skin antiseptic and as a skin wound protectant in the tentative final monograph for OTC topical antimicrobial drug products (January 6, 1978; 43 FR 1210 at 1229). This ingredient will be discussed further in the tentative final monograph for OTC first aid antiseptic drug products in a future issue of the **Federal Register.**

Reference

(1) OTC Volume 160186.

III. The Agency's Tentative Conclusions and Adoption of the Panel's Statements

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

1. Summary of Ingredient Categories

In the Miscellaneous External Panel's advance notice of proposed rulemaking for skin protectant drug products (47 FR 39436 at 39440 and 39448), the Panel stated that, although the agency's call-for-data notices (38 FR 31697 and 40 FR 38179) requested the submission of data and information for a number of specific active ingredients (47 FR 39436 at 39440 and 39448) or any other active ingredients used in OTC poison ivy and oak remedy drug products and insect bites drug products, the Panel reviewed only those ingredients with claims for preventing poison ivy, oak, or sumac or for treating insect bites by neutralization or inactivation of insect venom. As stated above, drug products for treatment of the symptoms of poison ivy-oak-sumac and insect bites are discussed in the external analgesic rulemaking published elsewhere in this issue of the **Federal Register** and will not be discussed further here.

The Panel received submissions for products containing a buffered mixture of cation and anion resins and for products containing ferric chloride that claimed to prevent poison ivy, oak, or sumac by complexing with the plant antigen before it enters the skin. The agency concurs with the Panel's determination that there are insufficient data to demonstrate the effectiveness of a buffered mixture of cation and anion resins in preventing poison ivy, poison oak, and poison sumac and agrees with the Panel's Category III classification of these ingredients. In addition, the agency concurs with the Panel's determination that there are no substantial data to support the safety and effectiveness of ferric chloride and agrees with the Panel's Category II classification of this ingredient.

The Panel also received submissions for products containing ammonium hydroxide and triethanolamine (trolamine) that claimed to neutralize or inactivate insect venom. The agency concurs with the Panel's determination that there are insufficient data to demonstrate the effectiveness of ammonium hydroxide and trolamine as insect bite neutralizers and concurs with the Panel's Category III classification of these ingredients.

Although the Miscellaneous External Panel mentioned the use of skin protectant ingredients for the prevention of poison ivy, poison oak, and poison sumac, and use as insect bite neutralizers, it did not review or classify all of the individual ingredients. Most of the ingredients in marketed products submitted to the Panel or ingredients that appeared in the call-for-data notices were simply listed in the Panel's statements on OTC drug products for the prevention of poison ivy, poison oak, and poison sumac (47 FR 39436 at 39440) and on OTC insect bite neutralizer drug products (47 FR 39448). The Panel noted at 47 FR 39440 that many of these ingredients labeled with claims as skin protectant drug products for symptoms of oozing or weeping due to contact dermatitis, poison ivy, or poison oak have been previously addressed by another OTC panel, the Topical Analgesic Panel. The agency has further considered the recommendations of the Topical Analgesic Panel on OTC skin protectant drug products (43 FR 34628), the tentative final monograph on OTC skin protectant drug products (48 FR 6820), and the additional data and information available at this time. Based upon this information, the agency is adding several active ingredients to the "Summary of Ingredient Categories" table for skin protectant active ingredients that appeared in the tentative final monograph for OTC skin protectant drug products (48 FR 6820 at 6831). These ingredients are ammonium hydroxide, buffered mixtures of cation and anion exchange resins, colloidal oatmeal, ferric chloride, polyvinylpyrrolidone-vinyl acetate copolymers, and trolamine. In addition, the agency is amending the entries for two ingredients that were listed as deferred and transferred to other rulemakings. These ingredients (corn starch and sodium bicarbonate) are now classified as skin protectants in this rulemaking. An updated table appears below for the convenience of the reader.

Summary of Ingredient Categories

Skin protectant active ingredients	Category
Allantoin[1]	I
Aluminum hydroxide gel	I
Ammonium hydroxide	III
Bismuth subnitrate	II
Boric acid	II
Buffered mixture of cation and anion exchange resins.	III
Calamine	I
Cocoa butter	I
Colloidal oatmeal [2]	I
Corn starch	III
Dimethicone	I
Ferric Chloride	II
Glycerin	I
Kaolin	I
Live yeast cell derivative [3]	III
Petrolatum	I
Polyvinylpyrrolidone-vinylacetate co-polymers.	II
Shark liver oil	I
Sodium bicarbonate	I
(a) for the temporary protection and relief of itching due to poison ivy/oak/sumac, and insect bites.	I
(b) for drying oozing and weeping	III
(c) as an insect bite neutralizer	II
Sulfur	II
Tannic acid	II
Trolamine [4]	III
White petrolatum	I
Zinc acetate [1]	I
Zinc carbonate	I
Zinc oxide	I

[1] Also classified by the Topical Analgesic Panel and the agency as a Category III wound healing agent.
[2] On condition that a standard chemical composition and concentration of the colloidal oatmeal can be established.
[3] Classified only as wound healing agent.
[4] Identified by the Miscellaneous External Panel as triethanolamine.

The Miscellaneous External Panel also listed a number of other ingredients in its statement that it said should be considered in other appropriate rulemakings for their use in treating poison ivy, poison oak, and poison sumac, and their related symptoms (47 FR 39436 at 39440). Except for the ingredients listed in the table above, no information has been provided on any of the other ingredients in the Panel's list. Accordingly, all of those ingredients are considered Category II.

The Miscellaneous External Panel also stated that it was not able to locate nor was it aware of data demonstrating the safety or effectiveness as OTC insect bite neutralizers of a number of active ingredients listed in its report (47 FR 39436 at 39448) and recommended a Category II classification for these ingredients. The agency concurs with the Panel's Category II classification of these ingredients for use as insect bite neutralizers.

2. Testing of Category II and Category III Conditions

The agency is not proposing specific testing guidelines in this document. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any skin protectant ingredient or conditions included in the review for the treatment and/or prevention of poison ivy, poison oak, and poison sumac as well as for the treatment and/or neutralization of insect bites, by following the procedures outlined in the agency's policy statement published in the **Federal Register** of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). That policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Changes

FDA has considered comments submitted to the Topical Analgesic Panel and the Miscellaneous External Panel, the submissions to the Miscellaneous External Panel, and other relevant information and concludes that it will tentatively adopt the substance of the Miscellaneous External Panel's statements. This Panel did not recommend a specific monograph for skin protectant drug products for use in the treatment and/or prevention of poison ivy, poison oak, and poison sumac or for the treatment and/or neutralization of insect bites. However, the Topical Analgesic Panel did recommend a monograph for skin protectant drug products (43 FR 34628), and the agency adopted this recommended monograph with some revisions in the tentative final monograph for OTC skin protectant drug products (48 FR 6820 at 6832). The agency is amending the tentative final monograph to include conditions for the treatment and/or prevention of poison ivy, poison oak, and poison sumac as well as for the treatment and/or neutralization of insect bites based on its evaluations of the data and its responses to the comments described above, and the other changes described in the summary below. A summary of the changes made by the agency follows.

1. The agency is proposing in § 347.3(d) of this tentative final monograph the following definition for poison ivy, poison oak, or poison sumac dermatitis: an allergic contact dermatitis (usually an intensely itching skin rash) due to exposure to plants of the genus *Rhus* (poison ivy, poison oak, poison sumac), which contain urushiol, a potent skin-sensitizing agent.

2. After reviewing all of the information submitted on the uses of sodium bicarbonate, the agency has decided to address sodium bicarbonate in the skin protectant rulemaking, not in the external analgesic rulemaking. Although the agency stated in the tentative final monograph for skin protectant drug products (48 FR 6820 at 6830) that it would address this ingredient in the external analgesic rulemaking, the agency finds that, because of its mechanism of action in relieving itching, i.e., its ability to form a mechanical barrier, it is appropriate to address sodium bicarbonate in the skin protectant rulemaking. (See comment 3 above.)

3. Based on the agency's review of data on colloidal oatmeal and the available information on sodium bicarbonate, the agency is revising the tentative final monograph to include these two ingredients as Category I skin protectant drug products and is proposing the following indication for these two ingredients in § 347.50(b)(4): "Provides temporary skin protection and relieves minor irritation and itching due to poison ivy, poison oak, poison sumac, and insect bites." However, for colloidal oatmeal, the agency states that sufficient data on the composition and concentration of the different constituents of this ingredient need to be established before it can be included in the final monograph. (See comments 1 and 3 above.)

4. The agency has added letter designations in § 347.10 *Skin protectant active ingredients* to include the addition of the ingredients colloidal oatmeal in paragraph (t) and sodium bicarbonate in paragraph (u). The agency has added these letter designations for these two active ingredients in appropriate paragraphs of § 347.50.

5. The agency is proposing to revise the statement of identity in § 347.50(a) to read as follows: (a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product with one or more of the following:

(1) "Skin protectant."

(2) *For products containing any ingredient in § 347.10 (b), (c), (g), (k), (l), or (m).* "Poison ivy, oak, sumac drying" (insert dosage form, e.g., "cream," "lotion," or "ointment").

(3) *For products containing any ingredient in § 347.10 (b), (c), (g), (k), (l), (m), (t), or (u).* "Poison ivy, oak, sumac treatment." (See comment 4 above.)

As noted above, an OTC skin protectant drug product may be labeled for one or more uses. Other uses for skin protectant active ingredients will be added to this monograph in the future, e.g., claims for the treatment and prevention of diaper rash. When the labeling of the product contains more than one labeled use, it must contain the appropriate statement(s) of identity, indications, warnings, and directions for each labeled use. For multiple use skin protectant drug products, the labeling appropriate to different uses may be combined to eliminate duplicate words and phrases so that the resulting information is clear and understandable. Introductory text to § 347.50 has been added in this amendment to reflect the above labeling requirements.

6. The agency is proposing that the warning in § 347.50(c)(1) "For external use only" not be required for sodium bicarbonate because this ingredient can be used orally for other purposes. (See comment 3 above.)

7. Because colloidal oatmeal can be slippery in a tub of water, the agency is proposing a warning in § 347.50(c)(9) when colloidal oatmeal is labeled for use as a soak in a tub, to read "Take special care to avoid slipping when getting into and out of the tub." (See comment 1 above.)

8. The agency is proposing directions in § 347.50(d)(2) for the use of colloidal oatmeal as a skin protectant, to read "Adults and children 2 years of age and over: *For use as a soak in a tub.* Turn

tub warm water faucet on to full force, then slowly sprinkle 1 cupful of colloidal oatmeal directly under the faucet into the tub. Before entering the tub, stir any colloidal oatmeal that may have settled to the bottom of the tub. Soak the affected area for 15 to 20 minutes as needed. Do not rub area dry, but instead pat dry so that a thin layer of the colloidal oatmeal will be left on the skin. Soak once or twice daily, or as directed by your doctor. Children under 2 years of age: Consult a doctor." (See comment 1 above.)

9. The agency is proposing directions in § 347.50(d)(3) for the use of sodium bicarbonate as a skin protectant, to read "Adults and children 2 years of age and over: Topical dosage is 1 to 100 percent sodium bicarbonate.

(i) *For use as a paste.* Add sufficient water to the sodium bicarbonate to form a paste and apply to the affected area of the skin as needed. Children under 2 years of age: Consult a doctor.

(ii) *For use as a soak in a tub.* Dissolve 1 to 2 cupfuls of this product in a tub of warm water and soak for 10 to 30 minutes as needed. Do not rub dry, but instead pat dry so that a thin layer of the sodium bicarbonate will be left on the skin. Children under 2 years of age: Consult a doctor." (See comment 3 above.)

(iii) *For use as a wet dressing.* Add sodium bicarbonate to water to make a solution. Use a container in which you can saturate a cloth. 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.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that not one of these rules, including this proposed rule for OTC skin protectant drug products for the treatment and/or prevention of poison ivy, poison oak, and poison sumac, as well as for the treatment and/or neutralization of insect bites is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act (Pub. L. 96–354). That assessment included a discretionary Regulation Flexibility Analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC skin protectant drug products for the treatment and/or prevention of poison ivy, poison oak, and poison sumac as well as the treatment and/or neutralization of insect bites is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invited public comment in the advance notice of proposed rulemaking regarding any impact that this rulemaking would have on OTC skin protectant drug products. No comments on economic impacts were received. Any comments on the agency's initial determination of the economic consequences of this proposed rulemaking should be submitted by January 31, 1990. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

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

Interested persons may, on or before January 31, 1990, submit to the Dockets Management Branch (address above) written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before January 31, 1990. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register**.

Interested persons, on or before October 3, 1990, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before December 3, 1990. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch. Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph for OTC skin protectant drug products, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on December 3, 1990. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register**, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

List of Subjects in 21 CFR Part 347

Labeling, Over-the-counter drugs, Skin protectant drug products.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, it is proposed that subchapter D of chapter I of title 21 of the Code of Federal Regulations be amended in Part 347 as proposed in the **Federal Register** of February 15, 1983 (48 FR 6820) as follows:

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

1. The authority citation for 21 CFR Part 347 continues to read as follows:

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

2. Section 347.3 is amended by adding new paragraph (d) to read as follows:

§ 347.3 Definitions.

* * * * *

(d) *Poison ivy, poison oak, or poison sumac dermatitis.* An allergic contact dermatitis (usually an intensely itching skin rash) due to exposure to plants of the genus *Rhus* (poison ivy, poison oak, poison sumac), which contain urushiol, a potent skin-sensitizing agent.

3. Section 347.10 is amended by adding new paragraphs (n), (o), (p), (q), (r), and (s) and reserving them and by adding new paragraphs (t) and (u) to read as follows:

§ 347.10 Skin protectant active ingredients.

* * * * *

(n)–(s) [Reserved]

(t) Colloidal oatmeal.

(u) Sodium bicarbonate, 1 to 100 percent.

4. Section 347.50 is amended by adding an introductory text paragraph, by revising paragraph (a), by adding new paragraph (b)(4), by revising paragraphs (c)(1), (c)(2), and (c)(3), by adding new paragraph (c)(9), and by revising paragraph (d) to read as follows:

§ 347.50 Labeling of skin protectant drug products.

A skin protectant drug product may have more than one labeled use. When the labeling of the product contains more than one labeled use, then the appropriate statement(s) of identity, indications, warnings, and directions must be stated in the labeling. For multiple use skin protectant drug products, the labeling appropriate to different uses may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product with one or more of the following:

(1) "Skin protectant."

(2) *For products containing any ingredient in § 347.10 (b), (c), (g), (k), (l), or (m).* "Poison ivy, oak, sumac drying" (insert dosage form, e.g., "cream," "lotion," or "ointment").

(3) *For products containing any ingredient in § 347.10 (b), (c), (g), (k), (l), (m), (t), or (u).* "Poison ivy, oak, sumac treatment."

(b) * * *

(4) *For products containing any ingredient in § 347.10 (t) and (u).* "Provides temporary skin protection and relieves minor irritation and itching due to poison ivy, poison oak, poison sumac, and insect bites."

(c) * * *

(1) "Avoid contact with the eyes."

(2) "If condition worsens or does not improve within 7 days, consult a doctor."

(3) *For products containing any ingredient in § 347.10 (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (m), and (t).* "For external use only."

* * * * *

(9) *For products containing colloidal oatmeal identified in § 347.10(t) when labeled for use as a soak in a tub.* "Take special care to avoid slipping when getting into and out of the tub."

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

(1) *For products containing any ingredient in § 347.10 (a), (b), (c), (d), (e), (f), (g), (h), (l), (j), (k), (l), or (m).* Apply liberally as often as necessary.

(2) *For products containing colloidal oatmeal identified in § 347.10(t).* Adults and children 2 years of age and over: *For use as a soak in a tub.* Turn tub warm water faucet on to full force, then slowly sprinkle 1 cupful of colloidal oatmeal directly under the faucet into the tub. Before entering the tub, stir any colloidal oatmeal that may have settled to the bottom of the tub. Soak the affected area for 15 to 20 minutes as needed. Do not rub area dry, but instead pat dry so that a thin layer of the colloidal oatmeal will be left on the skin. Soak once or twice daily, or as directed by your doctor. Children under 2 years of age: Consult a doctor.

(3) *For products containing sodium bicarbonate identified in § 347.10(u).* Adults and children 2 years of age and over: Topical dosage is 1 to 100 percent sodium bicarbonate.

(i) *For use as a paste.* Add sufficient water to the sodium bicarbonate to form a paste and apply to the affected area of the skin as needed. Children under 2 years of age: Consult a doctor.

(ii) *For use as a soak in a tub.* Dissolve 1 to 2 cupfuls of this product in a tub of warm water and soak for 10 to 30 minutes as needed. Do not rub dry, but instead pat dry so that a thin layer of the sodium bicarbonate will be left on the skin. Children under 2 years of age: Consult a doctor.

(iii) *For use as a wet dressing.* Add sodium bicarbonate to water to make a solution. Use a container in which you can saturate a cloth. 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.

* * * * *

Dated: August 26, 1989.

Frank E. Young,

Commissioner of Food and Drugs.

[FR Doc. 89-23262 Filed 10-2-89; 8:45 am]

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21 CFR Part 348

[Docket No. 78N-301P]

RIN 0905-AA06

External Analgesic Drug Products for Over-the-Counter Human Use; Proposed Rulemaking for Poison Ivy, Poison Oak, Poison Sumac, and Insect Bites Drug Products

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking amending the tentative final monograph (proposed rule) for over-the-counter (OTC) external analgesic drug products. The proposed rulemaking would establish conditions under which OTC external analgesic drug products for the treatment of the symptoms of poison ivy, poison oak, poison sumac, and insect bites are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the statements on OTC drug products for poison ivy, poison oak, and poison sumac, and for use as insect bite neutralizers of the Advisory Review Panel on OTC Miscellaneous External Drug Products, public comments on an advance notice of proposed rulemaking that was based on those statements, and public comments on the notice of proposed rulemaking for OTC external analgesic drug products. (See the **Federal Register** of February 8, 1983; 48 FR 5852.) The agency's proposals concerning the use of other OTC drug products for the treatment and/or prevention of poison ivy, poison oak, and poison sumac and for the treatment and/or neutralization of insect bites are being published elsewhere is this issue of the **Federal Register**. These proposals are part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed rulemaking before the Commissioner of Food and Drugs by

January 31, 1990. The agency is allowing a period of 120 days for comments and objections instead of the normal 60 days for the following reasons: (1) The concurrent publication of two rulemakings regarding OTC drug products for poison ivy, poison oak, poison sumac, and insect bites and (2) this document contains the first published evaluation of several submissions of data on OTC drug products for the treatment of symptoms of these conditions that were made to, but not reviewed by, the Advisory Review Panel on OTC Miscellaneous External Drug Products (Miscellaneous External Panel). New data by October 3, 1990. Comments on the new data by December 3, 1990. Written comments on the agency's economic impact determination by January 31, 1990.

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

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

SUPPLEMENTARY INFORMATION: In the **Federal Register** of September 7, 1982, FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), advance notices of proposed rulemaking and reopened the administrative records for OTC external analgesic drug products (47 FR 39412) and skin protectant drug products (47 FR 39436). The notices were published to allow for consideration of statements on OTC drug products for the prevention of poison ivy, poison oak, poison sumac, and for use as insect bite neutralizers. The statements were prepared by the Miscellaneous External Panel, which was the advisory review panel responsible for evaluating data on the active ingredients used for these conditions. Interested persons were invited to submit comments by December 6, 1982. Reply comments in response to comments filed in the initial comment period could be submitted by January 5, 1983.

In the **Federal Register** of December 28, 1982 (47 FR 57738), in response to a request for an extension of time, the comment period and reply comment period for OTC external analgesic drug products were extended to February 4, 1983, and to March 7, 1983, respectively.

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

One trade association and five drug manufacturers submitted comments concerning the use of external analgesic drug products for poison ivy, poison oak, poison sumac, and insect bites (poison ivy-oak-sumac and insect bites). Some of these comments were submitted to both the external analgesic and skin protectant rulemakings. In those cases where the same comments were submitted to both rulemakings, the comments will be addressed only in the appropriate amendment to either the proposed rule for OTC external analgesic drug products or for OTC skin protectant drug products published elsewhere is this issue of the **Federal Register.** Copies of the comments received are on public display in the Dockets Management Branch.

The Panel provided general statements on OTC drug products for the prevention of poison ivy, poison oak, poison sumac, and for use as insect bite neutralizers. However, the Panel did not review all of the submitted individual ingredients nor develop labeling for drug products for these indications. Also, the Panel reviewed only ingredients with labeling claims for prevention of poison ivy, poison oak, or poison sumac, or for treatment of insect bites by neutralization or inactivation of insect venom. However, many submissions to the Panel were for drug products used to treat the symptoms (i.e., itching, minor irritations) of poison ivy-oak-sumac and insect bites by the mechanism of depressing or stimulating cutaneous sensory receptors. Additionally, a number of external analgesic drug products labeled for the treatment of poison ivy-oak-sumac and insect bites were not submitted to the Miscellaneous External Panel. Therefore, the agency is expanding the scope of this segment of the external analgesic rulemaking to include all OTC external analgesic drug products labeled for any of these uses.

In this document, the agency is addressing comments concerning drug products for the treatment of symptoms of poison ivy-oak-sumac and insect bites when the mechanism of action involves the depression or stimulation of cutaneous sensory receptors. In the skin protectant rulemaking (published elsewhere in this issue of the **Federal Register**), the agency is addressing the claims for the treatment and/or prevention of poison ivy, poison oak, and poison sumac and for the treatment and/or neutralization of insect bites when the mechanism of action for these claims involves the ingredient's ability to neutralize or inactivate insect venom or the ingredient's ability to provide a mechanism barrier to protect the exposed skin surfaces from harmful or annoying stimuli.

In the **Federal Register** of February 8, 1983 (48 FR 5852), the agency published a tentative final monograph (proposed rule) for OTC external analgesic drug products. The agency issued this notice after considering the report and recommendations of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products (Topical Analgesic Panel) and public comments on an advance notice of proposed rulemaking that was based on those recommendations.

Interested persons were invited to submit comments by April 11, 1983, new data by February 8, 1984, and comments on new data by April 9, 1984. In response to that notice, one manufacturer's association and five drug manufacturers submitted comments concerning the use of external analgesic ingredients for the treatment of poison ivy-oak-sumac and insect bites. The agency is also addressing these comments in this notice of proposed rulemaking. Copies of the comments received are on public display in the Dockets Management Branch (address above).

In this notice of proposed rulemaking, FDA responds to public comment and further discusses its position on OTC external analgesic drug products for the treatment of poison ivy-oak-sumac and insect bites. Final agency action on this matter will occur with the publication at a future date of a final rule relating to OTC external analgesic drug products for the treatment of these conditions.

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

and III at the tentative final monograph stage.

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

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

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notices published in the **Federal Register** on December 12, 1972 (37 FR 26456), November 16, 1973 (38 FR 31697), and August 27, 1975 (40 FR 38179), or to additional information that has come to the agency's attention since publication of the advance notices of proposed rulemaking. The volumes are on public display in the Dockets Management Branch (address above).

I. The Agency's Tentative Conclusions on the Comments

The agency has reviewed the comments submitted to this rulemaking. As noted above, most of the comments were also submitted to the skin protectant rulemaking. Several of these comments are general in scope and will be addressed in this rulemaking for external analgesic drug products. Any of these general comments that are applicable to the skin protectant rulemaking are incorporated into that rulemaking.

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

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

2. Noting its continued opposition to FDA's exclusivity of labeling policy for OTC drugs, one comment stated that FDA should not prohibit the use of alternative OTC labeling terminology that is truthful, not misleading, and intelligible to the consumer. Another comment stated that its objections to FDA's "exclusivity" policy were presented at the agency's hearing on this subject on September 29, 1982.

In the **Federal Register** of May 1, 1986 (51 FR 16258), the agency published a final rule changing its labeling policy for stating the indications for use of OTC drug products. Under 21 CFR 330.1(c)(2), the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either (1) the specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "Approved Uses"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "Approved Uses"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "Approved Uses," plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All other OTC drug labeling required by a monograph or other regulation (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under the OTC drug monograph or other regulation where exact language has been established and identified by quotation marks, e.g., 21 CFR 201.63 or 330.1(g). The proposed rule in this document is subject to the labeling provisions of § 330.1(c)(2).

3. Two comments in response to the tentative final monograph for OTC external analgesic drug products (48 FR 5852) requested that specific indications for rashes caused by poison ivy be added to the monograph. One comment stated that the phrase "and rashes due to poison ivy, poison oak, or poison sumac" should be added to the indication "for the temporary relief of itching associated with sunburn, insect bites, or minor skin irritations." The comment requested that the agency revise this indication for external analgesic ingredients identified in § 348.10 (a), (b), and (c) to read "For the temporary relief of" (select one of the following: "pain," "itching," or "pain and itching") which may be followed by: "associated with" (select one or more of the following: "minor burns," "sunburn," "minor cuts," "scrapes," "insect bites," "minor skin irritations," or "rashes due to poison ivy, poison oak, or poison sumac"). The comment used the example of Category I combination products containing an external analgesic (antihistamine) and a skin protectant to support its request. The comment noted that the agency proposed the indication "Dries the oozing and weeping of poison ivy, poison oak, and poison sumac" in the skin protectant tentative final monograph (February 15, 1983; 48 FR 6820 at 6832). According to the comment, the purpose of a combination product containing a topical antihistamine and a skin protectant is both to help dry the poison ivy, poison oak, or poison sumac lesions and to relieve the itch associated with these conditions. The comment argued that not permitting an indication for the relief of itch associated with rashes due to poison ivy, poison oak, and poison sumac in the external analgesic monograph is not only inconsistent with the allowed combination but also misleading and would cause confusion to consumers.

The second comment stated that the proposed indication for external analgesic ingredients identified in § 348.10 (a), (b), and (c) of the tentative final monograph is too restrictive for the broad range of uses for these products. The comment proposed the following as an example of a truthful statement that is an appropriate indication for external analgesic drug products: "For the

temporary relief of pain and itching associated with poison ivy, poison oak, and poison sumac."

The agency agrees that indications for the relief of pain and itching associated with rashes due to poison ivy, poison oak, and poison sumac are appropriate for external analgesic ingredients identified in § 348.10 (a), (b), and (c).

The Topical Analgesic Panel recognized that the causes of pain and itch are multivaried but did not provide an exhaustive list of these causes in its report on OTC external analgesic drug products (December 4, 1979; 44 FR 69768 at 69776 and 69777). The Panel stated that itching is amenable to topically applied OTC external analgesic drug products that have antipruritic activity. The Panel explained that the anatomic pathways subserving pain and itch are identical and that itching results when cutaneous pain fibers are weakly stimulted, i.e., the difference between stimuli causing pain and itch is one of intensity. Further, the Panel stated that since the sensation of itch is mediated via pain fibers, local anesthetics and analgesics that block conduction along the axonal membranes, such as the nitrogenous drugs of the "caine" type and of the alcohol type, all have antipruritic activity. In addition, itching due to chemomediators can be relieved by drugs such as antihistamines that act competitively or combine with chemical agents released by trauma and other factors. The Panel recommended the following indication for external analgesic ingredients with antipruritic activity: "For the temporary relief of pain and itching due to minor burns, sunburn, minor cuts, abrasions, insect bites, and minor skin irritations."

In the tentative final monograph for OTC external analgesic drug products, the agency revised the Topical Analgesic Panel's recommended indication to allow the claim "For the temporary relief of itching" without listing examples of causes of itching (48 FR 5852 at 5863). The agency stated that such labeling would be clearly recognizable and meaningful to a consumer who was experiencing itching without knowing the cause. The agency also proposed in § 348.50(b)(2) the Topical Analgesic Panel's recommended list of examples of causes of itching as optional labeling as follows: "For the temporary relief of" (select one of the following: "pain," "itching," or "pain and itching") (which may be followed by: "associated with" (select one or more of the following: "minor burns," "sunburn," "minor cuts," "scrapes," "insect bites," or "minor skin irritations.")) At that time, the agency did not expand the Panel's recommended list of causes of itching to include poison ivy, poison oak, and poison sumac because it had not evaluated the Miscellaneous External Panel's recommendations on products for that use.

The agency believes that, as with other conditions that cause pain and itching, external analgesic drug products with antipruritic activity will help to relieve the pain and itching associated with rashes due to poison ivy, poison oak, and poison sumac. Poison ivy, poison oak, and poison sumac dermatitis is an allergic contact dermatitis that usually causes an intensely itching skin rash due to exposure to plants of the genus *Rhus* (poison ivy, poison oak, and poison sumac), which contain urushiol, a potent skin-sensitizing agent (Refs. 1 and 2). The agency believes that the pain and itching of rashes caused by contact of the skin with poison ivy, poison oak, or poison sumac are readily recognizable by the consumer. The agency accepts one comment's suggestion that the phrase "rashes due to" be included in the indications statement. However, because manifestations of contact with poison ivy, oak, or sumac or other than a rash, such as blistering, may be present and not all manufacturers may want to use the phrase "rashes due to" in the indications statement, the agency is proposing that the use of this phrase be optional.

The agency is therefore proposing that the indication in § 348.50(b)(2) be revised to read "For the temporary relief of" (select one of the following: "pain," "itching" or "pain and itching,") (which may be followed by: "associated with" (select one or more of the following: "minor burns," "sunburn," "minor cuts," "scrapes," "insect bites," "minor skin irritations," (optional, may include the following: "rashes due to") "poison ivy," "poison oak," or "poison sumac.")) This revised indication will also provide for consistent labeling of a combination product containing an external analgesic and a skin protectant, as noted by one comment.

In addition, the agency is proposing in § 348.3(g) of the tentative final monograph the following definition for poison ivy, poison oak, or poison sumac dermatitis: an allergic contact dermatitis (usually an intensely itching skin rash) due to exposure to plants of the genus *Rhus* (poison ivy, poison oak, poison sumac), which contain urushiol, a potent skin-sensitizing agent.

References

(1) "Dorland's Illustrated Medical Dictionary," 27th Ed., W. B. Saunders Co., Philadelphia, 1988, s.v. "rhus dermatitis."

(2) "Webster's New Collegiate Dictionary," G. & C. Merriam Co., Springfield, MA, 1979, s.v. "poison ivy."

4. One comment submitted data to the agency in support of claims for 3.6 percent ammonium hydroxide for the "relief of pain and itching from insect bites and discomfort due to nettle and berry bush scratches" (Ref. 1). In a later submission (Ref. 2), the company stated that the ingredient does not work by reducing inflammation or wheal size, nor is there any indication that it neutralizes insect venom. The company described a possible mechanism of action and concluded that the ingredient has a generalized antipruritic effect in relieving pain and itching that follow insect bites. The company noted the Topical Analgesic Panel's Category I classification of 1 to 2.5 percent ammonium hydroxide as a counterirritant (44 FR 69768 at 69792) and stated that the transcripts of the Panel's meetings show that members of that Panel recognized that ammonium hydroxide was effective for relief of itching due to insect bites. The company requested that 3.6 percent ammonium hydroxide be classified as a Category I antipruritic external analgesic ingredient in the final monograph for OTC external analgesic drug products.

Because the company has requested an antipruritic claim for all conditions included in the external analgesic tentative final monograph, the agency is not addressing the data in this document, which addresses only poison ivy-oak-sumac and insect bite claims. The agency will discuss the data regarding ammonium hydroxide in the final monograph for OTC external analgesic drug products in a future issue of the **Federal Register**.

References

(1) Comment No. C00046, Docket No. 78N-0301, Dockets Management Branch.

(2) Comment coded HER, Docket No. 78N-0301, Dockets Management Branch.

II. The Agency's Evaluation of the Submissions

The Miscellaneous External Panel reviewed only the use of OTC drug products for the prevention of poison ivy, poison oak, and poison sumac and for use as insect bite neutralizers. The Panel recommended that the agency consider in appropriate rulemakings ingredients and labeling claims submitted for treating poison ivy, poison oak, poison sumac, and their related symptoms (47 FR 39412 at 39417).

In this document, the agency discusses the use of OTC external analgesic drug products for the treatment of poison ivy-oak-sumac and insect bites. The agency has evaluated a number of submissions (Ref. 1) that were not reviewed by the Panel. Some of the submissions include drug products that are no longer marketed or that have been reformulated to include active ingredients and/or conditions that were proposed in the tentative final monograph for OTC external analgesic drug products (48 FR 5852). The manufacturers of these drug products have requested that their submissions or portions of their submissions concerning these drug products be withdrawn from further consideration in this rulemaking, as follows:

(1) Submissions (Ref. 2) concerning drug products containing pyrilamine maleate for the treatment of the symptoms of insect bites and/or poison ivy, poison oak, and poison sumac were withdrawn by the manufacturers (Refs. 3 and 4).

(2) A submission (Ref. 5) concerning a combination drug product containing chlorobutanol, glycerin, boric acid, salicylic acid, resorcinol, phenol, oxyquinoline sulfate, camphor, and 28 percent alcohol for the treatment of the symptoms of insect bites and poison ivy was withdrawn by the manufacturer (Ref. 6).

(3) A submission (Ref. 7) concerning a combination drug product containing benzocaine, phenol, and iodine for the treatment of the symptoms of insect bites and poison ivy was withdrawn by the manufacturer (Ref. 8).

(4) A submission (Ref. 9) concerning a combination drug product containing ethyl alcohol, gum camphor, oil of eucalyptus, and boric acid for the itch of insect bites and poison ivy, poison oak, and poison sumac was withdrawn by the manufacturer (Ref. 10).

(5) A portion of two submissions (Ref. 11) concerning drug products containing dexpanthenol in lotion form for the treatment of the symptoms of insect bites, poison ivy, and poison sumac was withdrawn by the manufacturer (Ref. 12).

References

(1) OTC Volumes 160006, 160076, 160104, 160124, 160204, and 160288.

(2) OTC Volumes 160074, 160080, 160132, 160156, and 160216.

(3) Letter from J. Wright, North Health Care, to W.E. Gilbertson, FDA, dated April 15, 1988, included in OTC Volume 06PIETFM.

(4) Letter from W.E. Byerley, Law Offices of W.E. Byerly, to *H. Cothran*, FDA, dated April 29, 1988, included in OTC Volume 06PIETFM.

(5) OTC Volume 160059.

(6) Letter from S. Smith, Dep Corp., to W.E. Gilbertson, FDA, dated May 3, 1988, included in OTC Volume 06PIETFM.

(7) OTC Volume 160278.

(8) Letter from M.H. Davis, Whitehall Laboratories, to W.E. Gilbertson, FDA, dated July 13, 1988, included in OTC Volume 06PIETFM.

(9) OTC Volume 160084.

(10) Letter from L. Sonopp, Clairol, to W.E. Gilbertson, FDA, dated June 9, 1987, included in OTC Volume 06PIETFM.

(11) OTC Volumes 160104 and 160204.

(12) Letter from A. Ryan, Armour Pharmaceutical Co., to L. Geismar, FDA, dated January 7, 1987, included in OTC Volume 06PIETFM.

5. One manufacturer submitted data in 1975 (Refs. 1 and 2) in support of the safety and efficacy of the combination of 2 percent dexpanthenol, 0.1 percent camphor, and 0.1 percent menthol "for use in mild eczemas and dermatoses; itching skin, minor wounds, stings, bites, poison ivy and poison oak (dry stage), minor skin irritations." The current labeling (submitted in 1987) contains the same indications, but lists dexpanthenol 2 percent as the only active ingredient (Ref. 3)

Because camphor and menthol are no longer listed as active ingredients in the product, the agency is addressing only dexpanthenol for use in the treatment of poison ivy-oak-sumac and insect bites in this comment. Dexpanthenol was not reviewed by any OTC advisory review panel for these uses.

The agency has evaluated one study on acute oral toxicity of dexpanthenol in male rats (Ref. 1). In a 14-day study, three preparations containing 2 percent dexpanthenol were orally administered to groups of six rats at a dose level of 50 milliliters per kilogram; no toxic or untoward effects, mortality, or loss of body weight occurred. However, the data provided no detailed information, and were neither blinded nor well-controlled. Dixon and Mastin (Ref. 4) treated 69 patients with various skin conditions of the lower extremities with a 2-percent dexpanthenol cream and reported that no evidence of sensitization was encountered. Likewise, no evidence of sensitization with the topical use of 2 percent dexpanthenol was observed by Welsh and Ede (Ref. 5) in 54 patients treated for dermatoses of various causes, by Kline and Caldwell (Ref. 6) in 31 patients treated for a variety of dermatoses, or by Kline (Ref. 7) in 500 dermatologic patients.

Regarding effectiveness, Dixon and Mastin (Ref. 4) cited 17 representative cases out of 69 patients and summarized the results in a table. In the table, the authors report some clinical evidence of relief of irritation and pruritus in a variety of skin diseases. However, none of the subjects had poison ivy, poison oak, poison sumac, or insect bites. Kline and Caldwell (Ref. 6) summarized 31 cases of various dermatoses treated with topical application of 2 and/or 5 percent dexpanthenol. The authors reported that many of the patients with skin diseases that cause itching obtained excellent results. However, none of the subjects had poison ivy, poison oak, poison sumac, or insect bites. The authors did state that further investigation of the topical application of this drug in other types of dermatoses is indicated. Kline (Ref. 7) reported 12 years of experience with topical dexpanthenol treatment of 500 dermatologic patients with a variety of itching dermatoses, including 84 patients with acute or chronic contact dermatitis (412 patients out of 500 or 82.4 percent obtained satisfactory results). However, none of the above studies were either blinded or well-controlled. Because no well-controlled safety or efficacy data were submitted to support topical use of 2 percent dexpanthenol for itching, such as that associated with poison ivy-oak-sumac or insect bites, the agency is classifying 2 percent dexpanthenol in Category III for safety and effectiveness for these uses.

Although the submitted labeling lists dexpanthenol as the active ingredient in the drug product, the United States Pharmacopeia recognizes both panthenol, which is a racemic mixture, and dexpanthenol, which is the dextro-form of panthenol (Ref. 8). Therefore, the agency is classifying both dexpanthenol and panthenol in Category III.

References

(1) OTC Volume 160104.

(2) OTC Volume 160204.

(3) Letter from A. Ryan, Armour Pharmaceutical Co., to L. Geismar, FDA, dated January 7, 1987, in OTC Volume 06PIETFM.

(4) Dixon, F. C., and M. N. Mastin, "The Use of Panthothenylol in Lower Extremity Lesions," *Journal of the National Association of Chiropodists*, 47:61–62 and 108, 1957.

(5) Welsh, A. L., and M. Ede, "Panthoderm: A Topical Therapeutic Adjuvant," *A.M.A. Archives of Dermatology and Syphilology*, 69:732–734, 1945.

(6) Kline, P. R., and A. Caldwell, "Treatment of Various Dermatoses with Topical Application of Panthenol," *New York State Journal of Medicine*, 52:1141–1143, 1952.

(7) Kline, P. R., "12 Years Experience Using Pantothenylol Topically," *Western Medicine*, 4:78–81, 1963.

(8) "United States Pharmacopeia XXI—National Formulary XVI," United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 296 and 781, 1985.

6. One comment submitted data to the Miscellaneous External Panel to support the safety and effectiveness of 1 to 2 percent diphenhydramine hydrochloride applied topically "for relief of itching due to insect bites, mild cases of sunburn, poison ivy or oak, and other minor skin irritations" and "for relief of itching due to mild poison ivy or oak, insect bites, or other minor skin irritations, and soothing relief of mild sunburn" (Ref. 1). The data included the results of three studies of a test product containing 1 percent diphenhydramine hydrochloride, calamine lotion, camphor, and 2 percent alcohol for the relief of itching caused by poison ivy/oak. In these studies, the antipruritic effect of diphenhydramine hydrochloride in the test product was compared with the antipruritic effect of calamine lotion alone as a control. The control did not contain diphenhydramine, camphor, or alcohol. According to the comment, the principal difference between the test product and the control is the presence of 1 percent diphenhydramine hydrochloride in the test product. No adverse reactions were reported in any of the studies.

The agency has evaluated the following three studies:

(1) Protocol 282–15 (Ref. 2) is a double-blind controlled study which included 45 subjects with a history of contact dermatitis (poison ivy/oak) with a pruritic component. To induce a contact dermatitis, poison ivy antigen patches were applied to both forearms and removed after 24 to 48 hours of contact with the skin. Both subjective and objective evaluations and examinations of the contact dermatitis were made. Subjects then applied the test product on one arm and the control containing calamine on the other arm every 3 hours and at night, as desired, for 3 consecutive days after development of contact dermatitis. After 3 days of observation, 84 percent preferred the test product for relief of itching. The investigators concluded that the test product reduced pruritus more than the control.

(2) Protocol 282–12 (Ref. 3) is a double-blind, randomized, controlled study. Poison ivy was induced with challenge patches in 50 subjects with a history of hypersensitivity to poison ivy. Twenty subjects with the most severe itching after the application of challenge patches were selected for the study. The test product was applied to one arm, and the control was applied to the other arm every 3 hours in six applications over a 24-hour period. Pruritus was assessed after each application. The investigator stated that a statistical analysis utilizing a t-test ($t_{19}=3.75$, $p<0.01$) strongly indicates that the antipruritic response with the use of the test product is significantly superior to the control.

(3) Protocol 282–10 (Ref. 4) is a double-blind, randomized, controlled study. Sixteen out of 29 subjects with artificially-induced poison ivy were studied after developing moderate to severely pruritic lesions. The test product was applied to one arm and the control was applied to the other arm every 3 hours for 48 hours. Pruritus was assessed after each application. The investigators found a significant difference ($p\leq0.05$) in favor of the test product.

The agency has determined that these studies were inappropriately designed because the test product contained camphor and alcohol but the control did not contain camphor and alcohol. The Topical Analgesic Panel has recommended (December 4, 1979; 44 FR 69768) and the agency has proposed (February 8, 1983; 48 FR 5852) that camphor be a Category I analgesic, anesthetic, and antipruritic at a 0.1- to 0.3-percent concentration. Because of the nature of the studies, it cannot be determined whether the 1 percent diphenhydramine hydrochloride, the camphor, or both provided the relief obtained. Although there is a problem with the study design, based on other information discussed below concerning the antipruritic properties of diphenhydramine hydrochloride, the agency believes that the above studies provide supporting evidence that 1 percent diphenhydramine hydrochloride relieves itching caused by poison ivy or oak.

The above data were not examined by the Miscellaneous External Panel in its statement on OTC drug products for the prevention of poison ivy, poison oak, and poison sumac. That Panel stated that ingredients such as diphenhydramine hydrochloride should be considered in other appropriate rulemakings for their use in treating poison ivy, poison oak, poison sumac, and their related symptoms. (See 47 FR 39412 at 39417 and 39440.) The Miscellaneous External Panel was aware that the Topical Analygesic Panel had reviewed similar data (Ref. 5) concerning the antipruritic effectiveness of 1 to 2 percent diphenhydramine hydrochloride and had recommended Category I status for this ingredient in its proposed monograph with the indication "For the temporary relief of pain and itching due to minor burns, sunburn, minor cuts, abrasions, insect bites, and minor skin irritations" (44 FR 69768 at 69865). In the tentative final monograph for OTC external analgesic drug products (48 FR 5852), the agency concurred with the Topical Analgesic Panel's recommendations and also agreed with a comment to that Panel's report that products containing antipruritic ingredients (including diphenhydramine hydrochloride) should be allowed to use the general indication "For the temporary relief of itching" without listing specific examples of the causes of the itching, or for itching associated with one or more causes. (See comment 28 at 48 FR 5863.) Section 348.50(b)(2) of the external analgesic tentative final monograph already provides the option of listing specific causes of itching such as "insect bites," "sunburn," and "minor skin irritations."

After reviewing the above data, the agency is now proposing to amend § 348.50(b)(2) to expand the list of optional causes of itching by adding "poison ivy," "poison oak," and "poison sumac." As revised, proposed § 348.50(b)(2) will now read as follows: *For products containing any external analgesic active ingredients identified in § 348.10 (a), (b), and (c).* "For the temporary relief of" (select one of the following: "pain," "itching," or "pain and itching") (which may be followed by: "associated with" (select one or more of the following: "minor burns," "sunburn," "minor cuts," "scrapes," "insect bites," "minor skin irritations," (optional, may include the following: "rashes due to") "poison ivy," "poison oak," or "poison sumac.")) (See also comment 3 above.)

References

(1) OTC Volume 160124.

(2) Protocol 282–15, draft of unpublished data, in OTC Volume 160124.

(3) Protocol 282–12, draft of unpublished data, in OTC Volume 160124.

(4) Protocol 282–10, draft of unpublished data, in OTC Volume 160124.

(5) OTC Volume 060095.

7. One manufacturer submitted data and information (Refs. 1 and 2) to the Miscellaneous External Panel on three combination drug products containing either 8 or 10 percent tannic acid and requested that these combinations be Category I for the temporary relief of itching associated with poison ivy, poison oak, or poison sumac. In addition to 10 percent tannic acid, one product contains 12.5 percent isopropanol as an active ingredient and is labeled "for temporary relief of itching associated with poison ivy, oak or sumac." A second product contains the following active ingredients: 10 percent tannic acid, 1.25 percent benzocaine, 0.4

percent camphor, 0.2 percent menthol, and 35 percent isopropanol, and is labeled "for the temporary relief of poison ivy-oak-sumac, sunburn, insect bites and other minor irritations." The third product contains the active ingredients 8 percent tannic acid, 0.5 percent benzocaine, 0.4 percent menthol, and 0.6 percent camphor, and is labeled "for the relief of minor pain and itching caused by poison ivy, poison oak, insect bites, sunburn and other minor skin irritations." The manufacturer stated that the tannic acid-isopropanol combination has been marketed since 1943, based on the findings of Schwartz and Warren (Ref. 3) and on informal testing by "local physicians," as a "'safe,' simple and economical product which helped to dry the blisters and relieved the itching due to poison ivy rash." The submissions included a 1949 "Federal Security Agency Public Health Service Health Information Series No. 65" publication that describes a method of using a 10-percent alcoholic solution of tannic acid to treat mild cases of poison ivy (Ref. 1). The manufacturer stated that the multicomponent combination drug products "were added as additional forms [of the original drug product] for the convenience of the users," and that all of the active and inactive components of the products have been acceptable to the medical profession and have been used in OTC drugs for many years. The manufacturer submitted several letters from consumers supporting the safety and effectiveness of these products and stated that it has an extensive file containing testimonials from satisfied customers confirming the effectiveness of its products. The submissions contained several studies on the safety of tannic acid or tannin and a table of summaries of several studies on the carcinogenicity of tannic acid (Refs. 2 and 4 through 8). The manufacturer concluded that 35 years of marketing experience with no serious complaints other than staining of the skin or clothing substantiates the fact that the products are safe and effective for the labeling claims. The manufacturer added that over this period of time its tannic acid-isopropanol product "has proven to be a mild, safe product to alleviate the discomforts of mild cases of poison ivy, sunburn, insect bites and minor skin irritations due to its astringent and protein precipitating properties." The manufacturer noted that it had compared its product "subjectively to every other leading OTC product on the market" and found its product to be at least as effective and generally more effective than other products, with no undesirable side effects.

The Topical Analgesic Panel reviewed tannic acid and stated that this ingredient is not safe for use as an OTC skin protectant (August 4, 1978; 43 FR 34628 at 34644). The Panel reviewed studies concerning the safety of topical use of tannic acid (Refs. 9, 10, and 11) and stated that the documented hepatotoxicity of tannic acid with repeated topical applications over large areas of damaged skin make this ingredient unsuitable for use as a skin protectant. In addition, the Panel stated that the desired effect of tannic acid, i.e., to produce a protein precipitate which would act as a protective coat (43 FR 34628 at 34644), causes the formation of an outer crust under which bacterial growth may flourish. The Miscellaneous External Panel and the agency concurred with the Topical Analgesic Panel's conclusions regarding the safety of tannic acid (47 FR 39412 at 39426 and 48 FR 6820 at 6825).

The manufacturer's summaries of some of the studies cited in support of the safety of tannic acid (Ref. 1) indicate that either no data were presented in the studies (Refs. 2 and 7) or the studies concerned the carcinogenic effect of tannic acid (Refs. 4, 6, and 8). One other study cited by the manufacturer (Ref. 5) was reviewed by the Topical Analgesic Panel in its discussion of tannic acid (43 FR 34628 at 34644). The Panel's evaluation of this study did not change its view that tannic acid is not safe for use as an OTC skin protectant. The studies cited in the submissions do not address the issues raised by the Panel, i.e., (1) that repeated use of tannic acid over large areas of damaged skin can cause liver damage, or (2) that formation of an outer crust on the skin (produced by the tannin's ability to precipitate protein) may allow bacteria to grow and flourish under the crust.

In addition, the information submitted on the effectiveness of 10 percent tannic acid to relieve itching of poison ivy-oak-sumac or insect bites is inadequate. The 1949 Public Health Service publication (Ref. 1) describes the use of a 10-percent alcoholic solution of tannic acid to treat mild cases of poison ivy, but does not present any data concerning the effectiveness of this solution. The 1941 Schwartz and Warren study (Ref. 3) involved "only 11 patients having dermatitis presumably caused by poison ivy," one of whom failed to return for final observation. The authors state that itching and discomfort in nine of the patients stopped within 1 or 2 days and all nine had recovered at the end of 1 week. The authors go on to state that the 10th patient, who did not fully recover for 2 weeks, was suspected of having dermatitis caused by crab grass, not poison ivy. This study does not support the effectiveness of 10 percent tannic acid because it is uncontrolled, the etiology of the dermatitis is uncertain, and objective methods of determining the effectiveness of the treatment are not described. In fact, the authors state that this treatment is reported in the hope that other physicians will give it a trial, and either confirm or disprove the efficacy of this treatment on a larger number of patients.

The testimonials included in the submissions are not adequate to establish effectiveness. The standards for establishing effectiveness in the OTC drug review state that isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered. (See 21 CFR 330.10(a)(4)(ii).)

Based on the above, the agency is placing 8 to 10 percent tannic acid in Category III for the temporary relief of itching associated with poison ivy-oak-sumac and insect bites. Therefore, any combination drug product that contains 8 to 10 percent tannic acid for these uses is also Category III.

With respect to the other active ingredients in the submitted combination drug products, 0.2 percent menthol and 0.4 percent camphor are Category I external analgesics and may be combined; isopropanol has not been classified as an external analgesic or as a skin protectant and would require adequate data to support its safety and effectiveness for such use; and although 5 to 20 percent benzocaine is Category I as an external analgesic, 0.5 to 1.25 percent benzocaine and any combination containing 0.5 to 1.25 percent benzocaine are Category III and would require adequate data to demonstrate effectiveness.

References

(1) OTC Volume 160076.

(2) OTC Volume 160288.

(3) Schwartz, L., and L. H. Warren, "Tannic Acid Treatment of Poison Ivy (Rhus Spp.) Dermatitis," *Public Health Reports*, 56:1039–1041, 1941.

(4) Armstrong, D. M. G., E. G. C. Clark, and E. Cotchin, "A Note on the Acute Toxicity of Hydrolyzable and Condensed Tannins," *The Journal of Pharmacy and Pharmacology*, 9:98–101, 1957.

(5) Korpassy, B., and M. Mosonyi, "The Carcinogenic Action of Tannic Acid: Effect of Casein on the Development of Liver Tumors," *Acta Morphologica Academiae Scientiarum Hungaricae*, 1:37–54, 1951.

(6) Krezanoski, J. Z., "Tannic Acid: Chemistry, Analysis, and Toxicology," *Radiology*, 87:655–657, 1966.

(7) Korpassy, B., and M. Mosonyi, "The Carcinogenic Activity of Tannic Acid; Liver Tumors Induced in Rats by Prolonged Subcutaneous Administration of Tannic Acid Solutions," *British Journal of Cancer*, 4:411–420, 1950.

(8) Robinson, H. J., and O. E. Graessle, "Toxicity of Tannic Acid," *Journal of Pharmacology*, 77:63–69, 1943.

(9) Wells, D. B., H. D. Humphrey, and J. J. Coll, "The Relation of Tannic Acid to Liver Necrosis Occurring in Burns," *The New England Journal of Medicine*, 226:629–636, 1942.

(10) Barnes, J. M., and R. J. Rossiter, "Toxicity of Tannic Acid," *The Lancet*, 2:218–222, 1943.

(11) McClure, R. D., C. R. Lam, and H. Romence, "Tannic Acid and the Treatment of Burns: An Obsequy," *Annals of Surgery*, 120:387–398, 1944.

8. One manufacturer (Ref. 1) submitted data and information for a product containing 0.5 percent tripelennamine hydrochloride, and 0.5 percent methapyrilene hydrochloride, and 0.1 percent menthol in combination with 0.0495 percent benzalkonium chloride with the labeling claims "Relieves itch and discomforts of skin allergies, hives, bee stings, nonpoisonous insect bites, poison ivy and oak, sunburn and minor skin disorders," and "Helps prevent skin infection." The comment subsequently informed the agency that it had reformulated its product by substituting 1 percent diphenhydramine hydrochloride for the 0.5 percent methapyrilene hydrochloride, but did not submit any additional data on the reformulated product (Ref. 2). The company subsequently submitted updated labeling stating that the active ingredients are diphenhydramine hydrochloride 1.0 percent, tripelennamine hydrochloride 0.5 percent, and benzalkonium chloride 0.12 percent and that menthol is an inactive ingredient (Ref. 3).

Two of the three active ingredients (tripelennamine hydrochloride and diphenhydramine hydrochloride) have been proposed as Category I for the temporary relief of pain and/or itching associated with insect bites and minor skin irritations in the tentative final monograph for OTC external analgesic drug products (48 FR 5852 at 5868). The Topical Analgesic Panel stated that there is evidence that topical creams containing 2 to 3 percent tripelennamine hydrochloride are effective in temporarily relieving the pruritus of poison ivy eruptions (44 FR 69768 at 69839). Based on the agency's discussion of poison ivy, poison oak, and poison sumac claims for all Category I antipruritic ingredients in comments 3 and 6 above, tripelennamine hydrochloride and diphenhydramine hydrochloride are being proposed as Category I ingredients for the temporary relief of pain and/or itch associated with poison ivy-oak-sumac, insect bites, and minor skin irritations. The agency proposed that benzalkonium chloride, the third active ingredient in the product, be classified Category III for use as a skin antiseptic and as a skin wound protectant in the tentative final monograph for OTC topical antimicrobial drug products (January 6, 1978; 43 FR 1210 at 1229). This ingredient will be discused further in the tentative final monograph for OTC first aid antiseptic drug products in a future issue of the **Federal Register**.

Proposed § 348.20(b)(2) of the external analgesic tentative final monograph provides for the combination of the antihistamine tripelennamine hydrochloride or diphenhydramine hydrochloride and any Category I topical antimicrobial active ingredient or combination identified in Part 333, when labeled for concurrent symptoms (48 FR 5852 at 5868). However, because the product described above contains two antihistamines, it does not qualify as a permitted combination included in § 348.20, nor does it meet the agency's combination policy for OTC drugs as stated in 21 CFR 330.10(a)(4)(iv) and in the agency's general guidelines for OTC drug combination products (Ref. 4). These guidelines state that Category I active ingredients from the same therapeutic category (antihistamines, in this case) that have the same mechanism of action should not ordinarily be combined unless there is some advantage over the single ingredients in terms of enhancing effectiveness, safety, patient acceptance, or quality of formulation. No data have been submitted demonstrating any of these advantages. Therefore, such a combination of ingredients is classified as Category III for treating poison ivy-oak-sumac and insect bites. Further, in a telephone conversation between representatives of the agency and the company, a company representative indicated that the diphenhydramine "was likely to be deleted" from the product at the time that a final order goes into effect (Ref. 5).

References

(1) OTC Volume 160006.

(2) Letter from H.W. Gordon, Commerce Drug Co., Inc., to W.E. Gilbertson, FDA, dated January 14, 1983, included in OTC Volume 06PIETFM.

(3) Letter from H.W. Gordon, Commerce Drug Co., Inc., to M. Benson, FDA, dated April 20, 1988, included in OTC Volume 06PIETFM.

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

(5) Memorandum of telephone conversation between H.W. Gordon, Commerce Drug Co., Inc., and M. Benson, FDA, dated March 3, 1983, included in OTC Volume 06PIETFM.

III. The Agency's Tentative Conclusions and Adoption of the Panel's Statements

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

1. Summary of Ingredient Categories

In the Miscellaneous External Panel's advance notice of proposed rulemaking for external analgesic drug products (47 FR 39412 at 39416 and 39430), the Panel stated that, although the agency's call-for-data notices (38 FR 31697 and 40 FR 38179) requested the submission of data and information for a number of specific active ingredients (47 FR 39412 at 39416 and 39430) or any other active ingredients used in OTC poison ivy and oak remedy drug products and insect bites drug products, the Panel reviewed only those ingredients with claims for preventing poison ivy, poison oak, or poison sumac or for treating insect bites by neutralization or inactivation of insect venom. As stated above, drug products for the treatment and/or prevention of poison ivy, poison oak, and poison sumac and for the treatment and/or neutralization of insect bites are discussed in the skin protectant rulemaking published elsewhere in this issue of the **Federal Register** and will not be discussed further here.

Although the Miscellaneous External Panel mentioned the use of external analgesic ingredients for the treatment of poison ivy-oak-sumac and insect bites, it did not review or classify all of the individual ingredients. Most of the ingredients in marketed products submitted to the Panel or ingredients that appeared in the call-for-data notices were simply listed in the Panel's statements on OTC drug products for the prevention of poison ivy, poison oak, and poison sumac (47 FR 39412 at 39416) and on OTC insect bite neutralizer drug products (47 FR 39412 at 39430). The Panel noted at 47 FR 39417 that many of these ingredients labeled with claims for the relief of minor skin irritations, itching, and rashes due to poison ivy, poison oak, and poison sumac have been previously addressed by another OTC panel, the Topical Analgesic Panel. The agency has further considered the recommendations of the Topical Analgesic Panel on OTC external analgesic drug products (44 FR 69768), the tentative final monograph on OTC

external analgesic drug products (48 FR 5852), and the additional data and information available at this time. Based upon this information, the agency is adding several active ingredients to the "Summary of Ingredient Categories" table for analgesic, anesthetic, and antipruritic active ingredients that appeared in the tentative final monograph for OTC external analgesic drug products (48 FR 5852 at 5865). These ingredients are benzocaine 0.5 to 1.25 percent, dexpanthenol, panthenol, and tannic acid. An updated table appears below for the convenience of the reader.

SUMMARY OF INGREDIENT CATEGORIES

Analgesic, anesthetic, and antipruritic active ingredients	Category
Aspirin	III
Benzocaine	
(a) 5 to 20 percent	III
(b) 0.5 to 1.25 percent	I
Benzyl alcohol	I
Butamben picrate	I
Camphor	I
Camphorated metacresol	II
Chloral hydrate	III
Chlorobutanol	III
Cyclomethycaine sulfate	III
Dexpanthenol	I
Dibucaine	I
Dibucaine hydrochloride	I
Dimethisoquin hydrochloride	I
Diphenhydramine hydrochloride	I
Dyclonine hydrochloride	III
Eugenol	III
Glycol salicylate	III
Hexylresorcinol	I
Hydrocortisone [1]	I
Hydrocortisone acetate [1]	I
Juniper tar	I
Lidocaine	I
Lidocaine hydrochloride	I
Menthol	II
Methapyrilene hydrochloride	III
Panthenol	I
Phenol	I
Phenolate sodium	I
Pramoxine hydrochloride	I
Resorcinol	III
Salicylamide	III
Tannic acid	I
Tetracaine	I
Tetracaine hydrochloride	III
Thymol	III
Trolamine salicylate [2]	I
Tripelennamine hydrochloride	III

[1] Hydrocortisone and hydrocortisone acetate are OTC external analgesics only for use as topical antipruritics.
[2] Identified by the Topical Analgesic Panel as triethanolamine salicylate.

The Miscellaneous External Panel's list of ingredients in marketed products for treating poison ivy, poison oak, poison sumac, and their related symptoms (47 FR 39412 at 39417) included a number of ingredients, with the exception of sodium bicarbonate, for *which no* information was provided. These ingredients are considered Category II. The agency is addressing sodium bicarbonate in the skin protectant document published elsewhere in this issue of the **Federal Register** because the mechanism of action of sodium bicarbonate involves the ingredient providing a mechanical barrier to protect the exposed skin surfaces from harmful or annoying stimuli.

2. Testing of Category II and Category III Conditions

The agency is not proposing specific testing guidelines in this document. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any external analgesic ingredients or conditions included in the review for the treatment of poison ivy-oak-sumac and insect bites by following the procedures outlined in the agency's policy statement published in the **Federal Register** of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). That policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Changes

FDA has considered comments submitted to the Topical Analgesic Panel and the Miscellaneous External Panel, the submissions to the Miscellaneous External Panel, and other relevant information and concludes that it will tentatively adopt the substance of the Miscellaneous External Panel's statements. This Panel did not recommend a specific monograph for external analgesic drug products for use in the treatment of poison ivy-oak-sumac and insect bites. However, the Topical Analgesic Panel did recommend a monograph for external analgesic drug products (44 FR 69768), and the agency adopted this recommended monograph with some revisions in the tentative final monograph for OTC external analgesic drug products (48 FR 5852 at 5867). In this document, the agency is amending that tentative final monograph to include conditions for the treatment of poison ivy-oak-sumac and insect bites based on its evaluations of the data and its responses to the comments described above. A summary of the changes made by the agency follows.

1. The agency is proposing in § 348.3(g) to add a definition for poison ivy, poison oak, or poison sumac dermatitis to the tentative final monograph. (See comment 3 above.)

2. The agency is amending proposed § 348.50(b)(2) ("Indications") by expanding the optional list of causes of itching to include "poison ivy," "poison oak," and "poison sumac" to read: "For the temporary relief of" (select one of the following: "pain," "itching," or "pain and itching") (which may be followed by: "associated with" (select one or more of the following: "minor burns," "sunburn," "minor cuts," "scrapes," "insect bites," "minor skin irritations," (optional, may include the following: "rashes due to") "poison ivy," "poison oak," or "poison sumac.")) (See comment 3 above.)

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that not one of these rules, including this proposed rule for OTC external analgesic drug products for the treatment of poison ivy-oak-sumac and insect bites, is a major rule.

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

The agency invited public comment in the advance notice of proposed rulemaking regarding any impact that this rulemaking would have on OTC external analgesic drug products. No comments on economic impacts were received. Any comments on the agency's initial determination of the economic consequences of this proposed rulemaking should be submitted by January 31, 1990. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

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

Interested persons may, on or before January 31, 1990, submit to the Dockets Management Branch (address above) written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before January 31, 1990. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register.**

Interested persons, on or before October 3, 1990, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before December 3, 1990. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch. Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph for OTC external analgesic drug products, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on December 3, 1990. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register,** unless the Commissioner finds good cause has been shown that warrants earlier consideration.

List of Subjects in 21 CFR Part 348

External analgesic drug products, Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, it is proposed that subchapter D of chapter I of title 21 of the Code of Federal Regulations be amended in part 348 as proposed in the **Federal Register** of February 8, 1983 (48 FR 5852) as follows:

PART 348—EXTERNAL ANALGESIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation for 21 CFR Part 348 continues to read as follows:

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

2. Section 348.3 is amended by adding new paragraph (g) to read as follows:

§ 348.3 Definitions.

* * * * *

(g) *Poison ivy, poison oak, or poison sumac dermatitis.* An allergic contact dermatitis (usually an intensely itching skin rash) due to exposure to plants of the genus *Rhus* (poison ivy, poison oak, poison sumac), which contain urushiol, a potent skin-sensitizing agent.

3. Section 348.50 is amended by revising paragraph (b)(2) to read as follows:

§ 348.50 Labeling of external analgesic drug products.

* * * * *

(b) * * *

(2) *For products containing any external analgesic active ingredients identified in § 348.10 (a), (b), and (c).* "For the temporary relief of" (select one of the following: "Pain," "itching," or "pain and itching") (which may be followed by: "associated with" (select one or more of the following: "minor burns," "sunburn," "minor cuts," "scrapes," "insect bites," "minor skin irritations," (optional, may include the following: "rashes due to") "poison ivy," "poison oak," or "poison sumac.")]

* * * * *

Dated: August 26, 1989.

Frank E. Young,

Commissioner of Food and Drugs.

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