§ 347.3 Definitions.

* * * * *

(e) [Reserved]

(f) *Fever blister, cold sore.* A vesicle that occurs at the junction of the mucous membrane and skin on the lips or nose and is caused by the virus *herpes simplex,* type 1.

3. Section 347.20 is amended by adding new paragraph (d) to read as follows:

§ 347.20 Permitted combinations of active ingredients.

* * * * *

(d) *Skin protectant and external analgesic combinations.* See § 348.20 of this chapter.

4. Section 347.50 is amended by adding new paragraph (a)(4), by redesignating paragraph (b)(2) as paragraph (b)(2)(i), and by adding new paragraph (b)(2)(ii) to read as follows:

§ 347.50 Labeling of skin protectant drug products.

* * * * *

(a) * * *

(4) For products containing any ingredient in § 347.10(a), (d), (e), (f), (h), (i), or (j). "Fever blister/cold sore treatment."

(b) * * *

(2) * * *

(ii) "Relieves dryness and softens cold sores and fever blisters," which may be followed by the optional statement, "Softens crusts (scabs) associated with cold sores and fever blisters."

* * * * *

Dated: December 25, 1989.

James S. Benson,

Acting Commissioner of Food and Drugs.

[FR Doc. 90-2164 Filed 1-30-90; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

21 CFR Part 348

[Docket No. 78N-301F]

RIN 0905-AA06

External Analgesic Drug Products for Over-the-Counter Human Use; Proposed Rulemaking for Fever Blister and Cold Sore Treatment 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 fever blisters and cold sores are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the statement of OTC drug products for the treatment of fever blisters by the Advisory Review Panel on OTC Miscellaneous External Drug Products, and public comments on an advance notice of proposed rulemaking that was based on that statement. The agency's proposals concerning the external use of other OTC drug products for treating fever blisters and cold sores are being published elsewhere is this issue of the **Federal Register.** Orally administered drug products for OTC use for the treatment of fever blisters are being addressed in a separate OTC drug rulemaking. The agency's proposals concerning those products were published in the **Federal Register** of June 17, 1985 (50 FR 25156). 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 May 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 fever blisters and cold sores and (2) this document contains the first published evaluation of several submissions of data on OTC drug products for the treatment 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 January 21, 1991. Comments on the new data by April 1, 1991. Written comments on the agency's economic impact determination by May 31, 1990.

ADDRESSES: Written comments, objections, new data, or requests for oral hearing to the Docket 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 Fisher 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 treatment of fever blisters. 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 this condition. 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, one physician, and five drug manufacturers submitted comments concerning the use of external analgesic drug products for the treatment of fever blisters and cold sores. Copies of the comments received are on public display in the Dockets Management Branch.

The Panel provided a general statement of OTC drug products for the treatment of fever blisters, but did not review individual ingredients and did not develop labeling for drug products for this indication. Several submissions to the Panel were for drug products used to treat the symptoms (i.e., itching, minor irritations) of fever blisters and cold sores by the mechanism of depressing or stimulating cutaneous sensory receptors. However, a number of external analgesic drug products labeled for the treatment of fever blisters and cold sores 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 fever blisters and cold sores when the mechanism of action for these uses involves the ingredient's causing

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 claims for the treatment of symptoms of fever blisters and cold sores when the mechanism of action for these claims involves the ingredient's ability to provide a mechanical barrier to protect 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, but it did not address products labeled for the treatment of cold sores and fever blisters. 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 4, 1984, and comments on new data by April 9, 1984. In response to that notice, a number of comments were submitted, but none of them concerned the specific use of external analgesic ingredients for the treatment of fever blisters and cold sores.

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 fever blisters and cold sores. 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 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 OCT drug rulemaking process before the establishment of a final monograph. Accordingly, FDA will not 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

1. One comment suggested that zinc sulfate as a 0.25 percent solution be considered for topical use as a Category I ingredient for the treatment of fever blisters. The comment noted that zinc sulfate was not contained in the marketed products submitted to the Miscellaneous External Panel, and as a result was not discussed. The comment pointed out that the National Institutes of Health (NIH) funded basic research, the results of which were not published until 1975 and 1977, which proved that zinc sulfate inhibited the synthesis of viral deoxyribonucleic acid (DNA) in cells infected with *herpes simplex* virus (HSV) (Refs. 1 and 2). The comment cited additional research funded by NIH (Ref. 3) as proving the selective inhibitory effect of zinc ions on the *herpes simplex* viral DNA polymerase. The comment mentioned an article by deRoetth (Ref. 4) as supporting topical application of 0.5 percent zinc sulfate solution as a highly effective treatment of Herpetic Keratitis, and cited the Merck Index (Ref. 5) as showing that zinc sulfate has been used in a concentration range of 0.2 to 1 percent as an astringent or styptic. The comment cited Brody (Ref. 6) as showing excellent results when concentrations of zinc sulfate solution less than 0.25 percent were applied to recurrent herpes simplex of the skin and oral mucous membrane. The comment mentioned an abstract (Ref. 7) supportive of zinc sulfate used in a concentration range of 0.025 to 0.05 percent as a solution for *herpes simplex* of the skin. The comment also provided pictures (Ref. 8) of patients treated topically with 0.25 percent zinc sulfate solution on their herpetic lesions. The comment concluded that zinc sulfate 0.25 percent in solution applied topically is safe, has been used to treat well over 100 patients without resultant skin irritation, and that a rapid drying and crusting of fever blisters results from its astringent activity.

The agency has reviewed the data submitted by the comment and determined that they are insufficient to classify zinc sulfate in Category I for the treatment of fever blisters. The submitted data show that zinc sulfate solution in a 0.2 to 1 percent concentration range applied topically produces an astringent effect on mucous membrane; however, the data are insufficient to demonstrate that zinc sulfate's astringent action is effective in the treatment of fever blisters. The studies (Refs. 1, 2, and 3) supportive of zinc inhibiting the synthesis of viral DNA in cells infected with HSV are in-vitro studies. Clinically-controlled in-vivo studies are needed to demonstrate that zinc sulfate causes a rapid drying and crusting of fever blisters. The effectiveness of 0.5 percent zinc sulfate solution against *herpes simplex* keratitis on the cornea (Ref. 4) is supportive, but is not a sufficient basis to extrapolate its effectiveness to the treatment of fever blisters in and around the mouth

because the skin around the mouth and the mucous membrane inside the mouth differ from the surface of the substance composing the cornea.

Brody (Ref. 6) studied 30 subjects with recurrent *herpes simplex* and post herpetic erythema multiforme who applied low concentrations (0.025 to 0.05 percent) of zinc sulfate solution 6 to 8 times a day to determine whether the solution would prevent relapse of the post-herpetic erythema multiforme. The results show that relapse was prevented without irritancy to the skin or mucous membranes; however, that success does not demonstrate the effectiveness of zinc sulfate in treating fever blisters. The abstract by Rees (Ref. 7) describes his use of a topical zinc solution in the treatment of herpes, but does not give his impression of its results. It lacks sufficient details to be useful. The comment's submission of patient pictures (Ref. 8) is also insufficient to support Category I status for zinc sulfate for the treatment of fever blisters.

The agency notes that the Merck Index (Ref. 5) states that zinc sulfate 0.2 to 1 percent topical solutions are irritating to the skin and mucous membrane. In addition, Brody (Ref. 6) also cites the Merck Index (Ref. 5) and states that for the skin and oral mucous membrane, these concentrations (0.2 to 1 percent) are too strong and cause irritation and an unpleasant dryness. Brody used concentrations in the 0.01- to 0.05-percent range in his studies. An appropriate safe concentration for the use of zinc sulfate in treating fever blisters needs to be determined.

Based on the above, the agency tentatively concludes that zinc sulfate in the concentrations considered has not been demonstrated as generally recognized as safe and effective for the treatment of fever blisters. The agency is classifying zinc sulfate in Category III and invites the submission of additional data.

References

(1) Gordon, Y., Y. Asher, and Y. Becker, "Irreversible Inhibition of Herpes Simplex Virus Replication in BSC–1 Cells by Zinc Ions." *Antimicrobial Agents and Chemotherapy*, 8:377–380, 1975.

(2) Shlomai, J., et al., "Effect of Zinc Ions on the Synthesis of Herpes Simplex Virus DNA in Infected BSC–1 Cells," *Virology*, 66:330–335, 1975.

(3) Fridlender, B., N. Chejanovsky, and Y. Becker, "Selective Inhibition of Herpes Simplex Virus, Type 1 DNA Polymerase by Zinc Ions," Virology, 84:551–554, 1978.

(4) deRoetth, A., "Treatment of Herpetic Keratitis," *American Journal of Ophthalmology*, 56:729–731, 1963.

(5) Stecher, P.G., editor, "The Merck Index," 8th Ed., Merck and Co., Rahway, NJ, p. 1130, 1968.

(6) Brody, I., "Topical treatment of recurrent herpes simplex and post-herpetic erythema multiforme with low concentrations of zinc sulphate solution," *British Journal of Dermatology*, 104:191–194, 1981.

(7) Rees, R.B., "Zinc Sulfate Topically for Herpes Simplex," *The Schoch Letter*, 31:35, 1981.

(8) Comment C00035, Exhibit F, Docket No. 78N–0301, Dockets Management Branch.

2. Two comments urged the agency to place tannic acid in Category I for use as an astringent in the treatment of fever blisters. One comment stated that the Panel decided not to review tannic acid as an astringent (47 FR 39412 at 39426), but instead reviewed it as an ingredient for use in the treatment of fever blisters because the only submission on tannic acid was for a product which is indicated in the treatment of fever blisters and cold sores (Ref. 1). The comment added that the Panel concluded that tannic acid was safe for OTC use for the treatment of fever blisters, but evidence of its effectiveness is inadequate (47 FR 39419). The comment cited the Panel (47 FR 39419) as recommending that human studies be conducted because the use of astringents may be a rational treatment in shortening the healing time of fever blisters. The comment also cited the Panel's statement that astringents are locally applied protein precipitants which have such a low cell penetrability that the action is essentially limited to the cell surface and the interstitial spaces (47 FR 39426). The comment contended that such action would clearly be rational in the treatment of a fever blister. The comment added that the drying action of an astringent would be rational because it would be useful in causing the blister to atrophy and would treat the sore if bleeding, cracking, or separation occurs. Noting the Panel's description of the complications of herpes blisters (47 FR 39419), the comment contended that the usefulness of an astringent in treating these possible complications is obvious under the Panel's own reasoning.

The comment argued that tannins are one of the principal types of astringents, that the Panel classified witch hazel in Category I for effectiveness as an astringent because of its tannin content (47 FR 39428), and thus tannic acid would be useful in drying the lesion caused by a fever blister or cold sore and would promote healing of the lesion. (The agency notes that although the term "tannin" is synonymous with "tannic acid," the official name "tannic acid" is being used in this document (Ref. 2).) The comment concluded that tannic acid is safe and effective for treating fever blister and does not require confirmation through unnecessary clinical studies.

The second comment supported its request by citing the Panel's statements at 47 FR 39426 that the affected area in contact with an astringent becomes drier, contending that such action would thus permit a fever blister to atrophy. The comment contended that this action would indicate tannic acid's effectiveness when applied to small areas of the lips to treat fever blisters.

In the amendment to the tentative final monograph for OTC skin protectant drug products used for treatment of fever blisters and could sores published elsewhere in this issue of the **Federal Register**, the agency discusses the use of tannic acid in the topical treatment of the symptoms of fever blisters and classifies it in Category III for safety and effectiveness. FDA believes that astringent properties may be useful in the treatment of the symptoms of fever blisters. However, the agency is concerned with potential oral mucosal absorption because of the proximity to the mucosal membranes of the oral cavity. Also, the agency is concerned about potential toxicity from oral ingestion, especially when eating and drinking, because of possible frequent applications of the drug to the lip and oral cavity. The agency that no efficacy studies were provided, nor did the manufacturer provide data to demonstrate the effectiveness to tannic acid alone in relieving the symptoms of fever blisters and cold sores.

The agency is aware that the Miscellaneous External Panel classified witch hazel in Category I as an astringent in the advance notice of proposed rulemaking and reopening of the administrative record for OTC external analgesic drug products published in the **Federal Register** of September 7, 1982 (47 FR 39412). The agency does not agree with the comments that the Panel attributed the astringent action solely to the tannins in witch hazel. The Panel stated that the effectiveness of witch hazel may be attributed to not only tannins, but possibly to the volatile oils and alcohol content in witch hazel (47 FR 39412 at 39428).

Although the agency acknowledges the concept of astringent properties as possibly being beneficial in alleviating the symptoms of fever blisters and cold sores, the agency believes that clinical data are needed to substantiate the effectiveness of the use of astringents in relieving these symptoms. In addition, based on the statement in the Merck Manual that "desiccating agents such a alcohol * * * are thought to fractionate

the herpes simplex virus, thereby inviting resistant and mutagenic strains" (Ref. 3), the agency has concerns about the relationship between the mechanism of action of astringents to precipitate protein in cells and the possible effect of the drug on the *herpes simplex* virus that causes the fever blisters. Further, in its discussion of cold sore treatment, the *Handbook of Non-Prescription Drugs* (Ref. 4) states that cold sore lesions should be protected from drying and fissuring because the cracking of the lesions may render them more susceptible to secondary bacterial infection, may delay healing, and usually increases discomfort. The handbook recommends that products that are highly astringent be avoided.

The agency concludes that data are needed to demonstrate tannic acid is safe and effective in relieving the symptoms of fever blisters and cold sores. In addition, because fever blisters generally occur in or around the mouth, the frequency and duration of application and oral toxicity levels of tannic acid need to be determined. Thus, the agency is classifying tannic acid for this use in Category III for both safety and effectiveness.

References

(1) OTC Volume 160012.

(2) Griffiths, M.C., editor, "USAN and the USP Dictionary of Drug Names", United States Pharmacopoeial Convention, Inc., Rockville, MD p. 533, 1989.

(3) Berkow, R., editor, "The Merck Manual", 15th Ed., Merck Sharp and Dohme Research Laboratories, Rahway, NJ, p. 2328, 1987.

(4) Baker, A.B., and D.K. Helling, "Oral Health Products" in "Handbook of Non-prescription Drugs", 8th Ed., American Pharmaceutical Association and The National Professional Society of Pharmacists, Washington, p. 492, 1986.

3. One comment requested that the following claims be added to the external analgesic monograph: for the temporary relief of discomfort of cold sores, fever blisters, sun blisters, and herpes or herpes labialis lesions" and "for relief from the discomfort of cold sores (herpes), sun and fever blisters." The comment contended that "the initial exposure (or longer exposure, i.e., 'overexposure') to stronger sunlight is the precipitating factor or cause of a 'fever blister/cold sore.' " The comment stated that, under such conditions, the consumer usually refers to herpes lip lesions as "sun blisters" (which they do not confuse with the same-named "sun-blisters" that may follow a sunburn). The comment added that its marketing experience indicates that sun exposure, as described above, is the major cause of herpes labialis. The comment supported use of the terms "herpes" and "herpes labialis" in OTC labeling on the Miscellaneous External Panel's statement at 47 FR 39418 which reads,

"Fever blisters" and "cold sores" are common names for herpes simplex, an acute infectious disease caused by the * * * virus *Herpes simplex*, type 1 * * *. The usual site of the lesion is at the junction of the mucous membrane and skin of the lips or nose. Hence, the term *herpes labialis* is frequently used.

The comment concluded that the terms "sun blisters," "herpes," and "herpes labialis" are acceptable OTC labeling when reference is clearly understood to be to the lips as it is with cold sores and fever blisters.

A second comment requested that the claim "For the temporary relief of discomfort of cold sores and fever blisters," be added to the external analgesic monograph for Category I analgesic/anesthetic/antipruritic ingredients in proposed § 348.10(b) and for Category I combinations in proposed § 348.20(b). The comment contended that part of the Panel's discussion of the treatment of fever blisters at 47 FR 39420 that "local anesthetics can relieve pain * * *" supports its request.

Prior to the publication of the external analgesic tentative final monograph (February 8, 1983; 48 FR 5852), the comment also requested that § 348.50(b)(2) of that tentative final monograph be amended to include fever blisters and cold sores, to read as follows, "For the temporary relief of pain and itching due to minor burns, sunburn, minor cuts, abrasions, insect bites, *fever blisters, cold sores,* and minor skin irritations." The comment also cited support from the Miscellaneous External Panel's statement at 47 FR 39420 that "local anesthetics can relieve pain * * *" as that statement related to fever blisters.

The agency disagrees with the first comment's position that the terms "sun blisters," "herpes," and "herpes labialis" are acceptable OTC labeling for the indications in this rulemaking. The agency believes that the term "sun blisters" could be misleading and that consumers may confuse the term with the condition associated with excessive sunburn. In addition, the comment did not present any data to demonstrate that consumers usually refer to herpes lip lesions as "sun blisters," and the agency is not aware of any such data.

The term "herpes" is too broad and may be misleading to the consumer who may associate the term with the genital form of herpes. Further, the term "herpes labialis" is not a term that is familiar to the general public. In addition, the agency has concerns that consumers may also confuse that term with the genital herpes condition. The Panel stated that the term "herpes labialis" is frequently used (47 FR 39412 at 39418), but did not indicate that the term was one that was common to the general public. The agency notes that the Panel did refer to "fever blisters" and "cold sores" as common names for herpes simplex. The agency believes that the terms "fever blisters" and "cold sores" are more readily recognized by the consumer and proposes that those terms be used in OTC drug product labeling.

In its discussion at 47 FR 39418, the Panel did not make any recommendations as to the Category I external analgesic ingredients considered to be safe and effective in the treatment of fever blisters. However, the Panel stated at 47 FR 39419 that recurrent herpes usually begins with a sensation of mild burning or itching and referred to a study where the researchers stated that the chief complaint from the subjects with fever blisters is pain. The Merck Manual describes fever blisters as "acute, painful vestibular eruptions of the oral mucosa or vermilion border * * *" and states that recurrent conditions begin with sensations of fullness, burning, and itching (Ref. 1). The agency believes that the comment's proposed claim "For the temporary relief of discomfort of cold sores and fever blisters" is too vague and does not inform the consumer of the specific symptoms to be relieved (i.e., pain and itching). Because the primary symptoms of fever blisters and cold sores are pain and itching, the agency agrees with the second comment and considers the proposed indication in § 348.50(b)(2), which states "For the temporary relief of" (select one of the following: "pain," "itching," or "pain and itching") * * * to be more appropriate for fever blisters. The agency is proposing to add § 348.50(b)(5) to include a paragraph for products containing any external analgesic active ingredient identified in § 348.10 (a) and (b) to read 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: "fever blisters," or "cold sores," or "fever blisters and cold sores")).

Reference

(1) Berkow, R. editor, "The Merck Manual," 15th Ed., Merck, Sharp and Dohme Research Laboratories, Rahway, NJ, p. 2327, 1987.

4. One comment requested that the following indication be added to the tentative final monograph on external

analgesic drug products for ingredients in proposed § 348.50(b) and combinations in proposed § 348.20: "Softens crusts (scabs) associated with cold sores and fever blisters." The comment contended that the claim conveys to the consumer the action of a product intended for this use and therefore should be acceptable OTC labeling. In support of its request, the comment cited the Miscellaneous External Panel's statement on OTC drug products for the treatment of fever blisters (47 FR 39412 at 39420):

> Although most viral infections cannot be cured by OTC drugs, fever blisters should not be neglected. Local anesthetics can relieve pain, antibiotics can control secondary bacterial infections when they occur, and ointments (protectants) can soften crusts * * *. Drying agents such as alcohols, astringents, or skin protectant agents may be useful.

The agency notes that in the above statement the Panel said that local anesthetics are used to relieve pain and that ointments (protectants) can soften crusts. The comment did not present, and the agency is not aware of, any data that demonstrate that external analgesic ingredients soften crusts (scabs) associated with cold sores and fever blisters. Therefore, this claim will not be added to the external analgesic monograph. The use of skin protectant ingredients to soften crusts (scabs) associated with cold sores and fever blisters is discussed in comment 2 of the tentative final mongraph for OTC skin protectant drug products for the treatment of fever blister and cold sores, published elsewhere in this issue of the **Federal Register.**

5. One comment suggested that the combination policy proposed in § 348.20(c) be amended to allow a combination of an external analgesic and a sunscreen for treatment and prevention of fever blisters and cold sores. The comment contended that any generally recognized safe and effective sunscreen is useful in the prevention and treatment of cold sores and fever blisters. Noting that the combination of an external analgesic and a sunscreen has been proposed as a Category II combination in the external analgesic rulemaking (December 4, 1979; 44 FR 69768 at 69790), the comment contended that for limited use on the lips, cold sores, and fever blisters, the combination should be placed in Category I.

The comment added that the usefulness of a sunscreen agent in preventing these blisters and lesions is evident from the Miscellaneous External Panel's own reasoning. The comment cited the Panel's statement that "such events as fever, chilling, sunburn, windburn, menstruation, upset stomach or gastrointestinal disturbance, emotional stress or excitement may reduce the immune state sufficiently for the virus to become activated and again cause an infection, designated recurrent herpes" (47 FR 39412 at 39419). The comment also cited the report on Orally Administered Drug Products for the Treatment of Fever Blisters for OTC Human Use by the Advisory Review Panel on OTC Miscellaneous Internal Drug Products in which the Panel stated that exposure to sunlight could cause recurrent herpes (January 5, 1982; 47 FR 504).

The comment further contended that persons prone to "sun blisters" should avoid undue exposure to sunlight in the ultraviolet light range, which is thought to be the precipitating factor; namely, 290 nanometers up to and through the visible light wavelengths. The comment stated that this excess exposure can be reduced with the use of effective topical sunscreens.

The comment argued that products containing combinations of Category I external analgesic and sunscreen ingredients should thus be recognized as safe and effective for the prevention and relief of discomfort of fever blisters, sun blisters, and cold sores (herpes). While the comment acknowledged that the combination of an external analgesic and a sunscreen for use over the majority of the body may be irrational for the reasons discussed by the Topical Analgesic Panel, it contended that for the limited use on the lips, cold sores, and fever blisters the combination is not only rational but medically prudent. The comment added that this combination would meet the Topical Analgesic Panel's general combination policy (44 FR 69768 at 69785), which states:

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

The comment claimed that it has marketing experience to support the claim that effective protection from the sun can help prevent sun-induced herpes or lip "sun blisters."

The comment urged that § 348.20(c) be amended to include a paragraph to the effect that:

> The active ingredients of the combination product consist of any single active ingredient identified in either (b)(1)(i), (b)(1)(ii), or (b)(2) of this section, or any combination identified in paragraph (b) of this section, and any generally recognized safe and effective sunscreen active ingredient provided the product is labeled for the concurrent symptoms involved, e.g., "For the temporary relief of pain and itching due to fever blisters, cold sores, canker sores, and other mouth sores and to help prevent the development or recurrence of these blisters and sores.

The comment requested the following indications for the external analgesic-sunscreen combination product: "Protects and helps prevent sun and fever blisters caused by overexposure to the sun," and "Filters (or screens or blocks [if applicable]) out the sun's rays to help prevent (lip) sun blisters." The comment contended that these claims convey the action of the drug product to the consumer and should be acceptable OTC labeling.

The agency acknowledges the statements made by the Miscellaneous Internal Panel and by the Miscellaneous External Panel concerning the effect of sunlight on causing recurrent herpes. However, those statements are not substantiated by supportive data that show that the use of a sunscreen will either treat or prevent fever blisters or cold sores. The agency's combination policy requires that each ingredient in the product make a contribution to the product's claimed effect. Data from clinical studies are needed to demonstrate that a combination product containing an external analgesic ingredient and a sunscreen ingredient is needed for concurrent administration and to support the role of the sunscreen ingredient, which appears to be prevention, while the external analgesic ingredient is relieving discomfort. The agency is classifying the combination of an external analgesic and a sunscreen ingredient in Category III, and invites the submission of data in support of the comment's contention that sunlight causes "sun blisters," and that a sunscreen will prevent their recurrence. Data are also needed to demonstrate that a target population exists which can benefit from concurrent use of the two types of ingredients in the same product. The claims requested by the comment will be considered when adequate supporting data for the combination product have been submitted.

6. One comment urged the agency to allow a combination of a Category I external analgesic, topical antimicrobial, and astringent for the treatment of fever blisters and cold sores. The comment contended that because treatment of

pain, prevention of infection, and the drying action of an astringent are all useful in the treatment of fever blisters and cold sores (as mentioned by the Miscellaneous External Panel at 47 FR 39420), the combination of these 3 types of ingredients should be placed in Category I. In support of its contention, the comment cited the combination policy set forth in the advance notice of proposed rulemaking for OTC external analgesic drug products (44 FR 69768 at 69785) which states that an OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population. The comment quoted the Topical Analgesic Panel's statements at 44 FR 69785 and underlined one part as follows:

> The panel not only concurs with, but strongly supports this regulation, and believes that each active ingredient in a combination product must contribute to the claimed effect, and that the combination must provide rational concurrent therapy. It is the view of the Panel that it is irrational to use a combination product unless each of its active ingredients contributes to the effective treatment of at least one of the labeled symptoms for which the combination of ingredients is recommented. The specific combination should be at least as safe and effective as therapeutic doses of the individual active ingredients when used alone.

The comment noted that the Topical Analgesic Panel had recommended a combination of an external analgesic and a topical antimicrobial as a Category I combination in § 348.20(c)(2) at 44 FR 69865. The comment added that the three-ingredient combination that it was requesting would be a rational combination based on the external analgesic rulemaking and 21 CFR 300.50. Accordingly, the comment urged that proposed § 348.20(c) be amended to include a paragraph to the effect that:

> The active ingredients of the combination product consist of any single active ingredient identified in either (b)(1)(i), (b)(1)(ii), or (b)(2) of this section, or any combination identified in paragraph (b) of this section, and any generally recognized safe and effective topical antimicrobial active ingredient or topical antimicrobial combination, and any generally recognized safe and effective topical astringent ingredient, provided the product is labeled for the concurrent symptoms involved, e.g., for the temporary relief of pain and itching due to fever blisters, cold sores, canker sores, and other mouth sores and to promote healing and to protect against contamination of the sore.

In the tentative final monograph for OTC external analgesic drug products, the agency proposed that a combination of an external analgesic active ingredient in § 348.10 (a), (b), or (c) with a topical antimicrobial active ingredient or topical antimicrobial combination be Category I (48 FR 5852 at 5868). In this tentative final monograph, the agency is not proposing a combination of an external analgesic active ingredient identified in § 348.10 (a), (b), or (c) and any generally recognized safe and effective topical antimicrobial active ingredient or topical antimicrobial combination for the treatment of cold sores and fever blisters. In the notice of proposed rulemaking for OTC skin protectant drug products for the treatment of fever blisters and cold sores appearing elsewhere in this issue of the **Federal Register**, the agency explained in comment 3 that it lacks sufficient data to demonstrate the effectiveness of antimicrobial ingredients against fever blisters and cold sores. Accordingly, the agency classified in Category III for the treatment of fever blisters or cold sores any combination of a Category I skin protectant active ingredient in proposed § 347.10 (a) and (b) and a Category I antimicrobial active ingredient identified in part 333, subpart A. Similarly, because of the lack of data on claims for promoting healing and protecting against contamination of the sore, the agency is classifying in Category III any combination of an external analgesic active ingredient in proposed § 348.10 (a) and (b) and a Category I antimicrobial active ingredient or topical antimicrobial combination identified in part 333, subpart A. The agency invites the submission of data in support of any such combinations in treating fever blisters and cold sores.

Additionally, the safety and effectiveness of a combination of these two types of ingredients with an astringent has not been established, as the comment suggests. The agency is not aware of any data showing that an astringent would add anything to the combination. The benefit of adding an astringent to the combination of an external analgesic and an antimicrobial needs to be established. Therefore, at this time, the agency is also classifying the combination of an external analgesic, a topical antimicrobial, and an astringent in Category III.

7. One comment requested that § 348.20 of the tentative final monograph on OTC external analgesic drug products be amended to include a combination of a Category I astringent and an external analgesic ingredient provided that such products are appropriately labeled for both classes of ingredients. The comment contended that the Panel was aware that OTC ingredients are used on lesions amenable to treatment by external analgesics and astringents.

In the advance notice of proposed rulemaking for OTC astringent drug products, published in the **Federal Register** of September 7, 1982 (47 FR 39412), the Miscellaneous External Panel stated that it concurred with the FDA guidelines for OTC combination products which state that Category I active ingredients from different therapeutic categories may be combined to treat different symptoms concurrently only if each ingredient is present within its established safe and effective dosage range and the combination meets the OTC combination policy in all other respects (see 47 FR 39430). Although the Panel was aware of OTC drug products which combine various ingredients with an astringent (47 FR 39429), the Panel did not recommend any such combinations nor did it specifically mention combinations of an external analgesic with an astringent.

In the tentative final monograph for OTC astringent drug products that amends the tentative fnal monograph for OTC skin protectant drug products (54 FR 13490), the agency stated that it had surveyed the OTC drug marketplace and determined that such combinations are currently being marketed with claims such as for the temporary relief of itching or for anal/perianal itching and discomfort. Combinations of an external analgesic and an astringent were proposed as Category I for these uses in the tentative final monograph for OTC anorectal drug products, published in the **Federal Register** of August 15, 1988 (53 FR 30756).

In response to the comment's request to include the combination of an external analgesic and an astringent in the tentative final monograph for OTC external analgesic drug products, the agency has surveyed the OTC drug marketplace to determine if such products exist for use in the treatment of fever blisters and cold sores. The agency has identified some product containing a combination of several active ingredients that include an external analgesic and an astringent (Refs. 1 and 2). However, none of these products contain only an external analgesic and

an astringent. The comment did not provide information on any specific products to containing an external analgesic and an astringent, on the symptoms/conditions to be treated concurrently, or on the proposed labeling for such combinations. Further, the comment did not submit any data to support the combination of an external analgesic and an astringent in relieving the symptoms of fever blisters and cold sores.

The agency has questioned the safety and effectiveness of astringents in alleviating the symptoms of fever blisters (see comment 2 above), and has classified the use of an astringent in treating the symptoms of fever blisters and cold sores in Category III at this time. (See comment 6 in the amended tentative final monograph on OTC skin protectant drug products published elsewhere in this issue of the **Federal Register**.) Based on the above, the agency is classifying a combination of an external analgesic and an astringent ingredient for use in the topical treatment of the symptoms of fever blisters and cold sores in Category III.

References

(1) Physicians' Desk Reference for Nonprescription Drugs, 8th Ed., Medical Economics Co., Inc., Oradell, NJ, p. 547, 1987.

(2) Baker, A.B., and D.K. Helling, "Oral Health Products" in "Handbook of Nonprescription Drugs," 8th Ed., American Pharmaceutical Association and The National Professional Society of Pharmacists, Washington, p. 505, 1986.

II. The Agency's Evaluation of the Submissions

The Miscellaneous External Panel discussed only in general the use of OTC drug products for the treatment of fever blisters and cold sores. The Panel recommended that the agency consider in appropriate rulemakings ingredients and labeling claims submitted for treating fever blisters, cold sores, and their related symptoms (47 FR 39412 at 39418).

In this document, the agency discusses the use of OTC external analgesic drug products for the treatment of fever blisters and cold sores. The agency has evaluated eight submissions (Ref. 1) that were not reviewed by the Panel. Two manufacturers have requested that their submission (Refs. 2 through 8) be withdrawn from further consideration for all claims (Refs. 9 and 10). One manufacturer's submission concerned drug products containing stabilized aloe vera gel for topical use for numerous indications, including the treatment of fever blisters (Refs. 2 through 7). The other manufacturer's submission concerned a liquid product with several labeling claims, one of which was "helps relieve itching and irritation of cold sores." The product contained alcohol, boric acid, chlorobutanol, camphor, glycerin, oxyquinoline sulfate, phenol (liquefied), resorcinol, and salicylic acid (Ref. 8).

References

(1) OTC Volumes 160008, 160096, 160136, 160197, 160208, 160218, 160225, and 160278.

(2) OCT Volume 160252A.

(3) OTC Volume 160252B.

(4) OTC Volume 160273.

(5) OCT Volume 160274.

(6) OTC Volume 160422.

(7) OCT Volume 160423.

(8) OCT Volume 160059.

(9) Letter from A. J. Davis, Aloe Vera of America, Inc., to W.E. Gilberston, FDA, dated May 20, 1988, in OTC Volume 06FBETFM, Docket No. 78N-301F, Dockets Management Branch.

(10) Letter from S. Smith, Dep Corporation, to W.E. Gilbertson, FDA, dated May 3, 1988, in OTC Volume 06FBETFM, Docket No. 78N-301F, Dockets Management Branch.

8. One comment requested that two products, a surgical dressing and a cream containing a complexed mixture of camphor and metacresol in a 3:1 weight ratio, be classified in Category I as a local topical anesthetic for the relief of fever blisters. The comment contended that results of numerous studies and clincial tests submitted to other advisory review panels (Ref. 1) showed that the complex has a strong desensitizing and topical anesthetizing effect. The comment added that its two products have been marketed for almost 50 years, that its customers are primarily health-care professionals, and that there have been virtually no negative comments (adverse reactions and/or lack of effectiveness) on the products. The comment provided labeling for the two products; however, no claim for treatment of fever blisters appears on the submitted labeling.

Camphorated metacresol has been extensively reviewed in the external analgesic rulemaking and was proposed as a Category I ingredient for topical use in the tentative final monograph on OTC external analgesic drug products (48 FR 5852; February 8, 1983). The agency has considered which previously proposed Category I external analgesic ingredients would be appropriate to use on cold sores and fever blisters and is proposing camphorated metacresol as Category I for relief of pain and/or itch of cold sores or fever blisters in this tentative final monograph. (See discussion in comment 14 below.)

Reference

(1) OTC Volume 160225.

9. A manufacturer submitted data (Refs. 1, 2, and 3) to the Miscellaneous External Panel on two products (a liquid and a powder dosage form) containing a complex formed by combining camphor with phenol. The labeling for the liquid product contains an indication, "relieves discomforts, helps to heal * * * fever blisters, cold sores * * *" among other indications. The powder product is labeled under the heading "For dry dressings and prickly heat:" "For * * * cold sores, fever blisters * * *" among other indications. The liquid product contains camphor 10.8 percent complexed with phenol 4.7 percent in a light mineral oil vehicle. The powder product contains camphor 4.4 percent combined with phenol 2 percent.

Camphor 10.8 percent complexed with phenol 4.7 percent in a light mineral oil, U.S.P. vehicle has been extensively reviewed in the external analgesic rulemaking and was proposed as a Category I ingredient for topical use in the tentative final monograph on OTC external analgesic drug products (48 FR 5852; February 8, 1983). The agency has considered which previously proposed Category I external analgesic ingredients would be appropriate to use on cold sores and fever blisters and is including camphor 10.8 percent complexed with phenol 4.7 percent in a light mineral oil, U.S.P. vehicle for relief of pain and/or itch of cold sores or fever blisters in this tentative final monograph. (See discussion in comment 14 below.)

The agency notes that no information was provided to show that the camphor and phenol are present in a complex in the powder product. If a complex does not exist, the 2-percent concentration of phenol in the powder exceeds the 1.5-percent maximum concentration of phenol that was proposed as Category I in the tentative final monograph for OTC external analgesic drug products (48 FR 5852 at 5867). In addition, camphor at 4.4 percent exceeds the 3 percent maximum concentration as an individual ingredient for analgesic, anesthetic, and antipruritic use proposed in the tentative final monograph for OTC external analgesic drug products (48 FR 5867). Further, it is not clear how the prowder product would be used as a dry dressing (as stated in its labeling) on cold sores and fever blisters. Finally, the agency is aware that the powder product has not been marketed for a number of years (Ref. 4). Based on the above, the agency is classifying camphor 4.4 percent and phenol 2 percent as a powder for external analgesic use on fever blisters and cold sores in Category II.

References

(1) OTC Volume 160136.
(2) OTC Volume 160208.
(3) OTC Volume 160218.
(4) Memorandum of telephone conversation, June 8, 1989, between K. Bucko, Sterling Winthrop Co., and M.T. Benson, FDA, in OTC Volume 06FBETFM, Docket No. 76N-301F, Dockets Management Branch.

10. One manufacturer submitted data (Ref. 1) to the Miscellaneous External Panel for a combination product containing 6.37 percent benzocaine, 0.45 percent phenol, and 0.15 percent iodine with several labeling claims, one of which was for the temporary relief of discomfort of fever blisters and cold sores. According to the manufacturer, benzocaine was included in the product for its properties as a topical anesthetic to relieve pain attributed to cold sores and fever blisters, and the phenol and iodine were included as antiseptic agents. The submission included the results of animal studies to determine dermal and gingival toxicity in rabbits, literature references containing human safety data, and other literature references containing efficacy data. Subsequently, the manufacturer submitted updated labeling (Ref. 2) showing that the active ingredients of the product are benzocaine 6.3 percent, phenol 0.5 percent, and alcohol 70 percent. The manufacturer stated that the product had been reformulated since the original submission was made in 1978, and iodine is now an inactive ingredient. Subsequently, the manufacturer informed the agency that the product contains povidone iodine 0.48 percent stabilized with potassium iodide 1 percent to give 0.05 percent available iodine, with a labeled quantity of 0.04 percent to cover loss in manufacturer (Ref. 3). The manufacturer stated that iodine is included as a flavorant.

The ingredients contained in the currently marketed product when applied to the oral mucosa were reviewed and evaluated by the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products (Dental Panel) in its report on OTC drug products for the relief of oral discomfort (May 25, 1982; 47 FR 22712), and by the Advisory Review Panel on OTC Oral Cavity Drug Products (Oral Cavity Panel) in its report on OTC oral health care drug products (May 25, 1982; 47 FR 22760). Both panels classified benzocaine as an oral mucosal analgesic and as an anesthetic/analgesic in Category I in a 5- to 20- percent concentration range. The Dental Panel classified phenol as an oral mucosal analgesic in Category I in a 0.25- to 1.5-percent concentration range. The Oral Cavity Panel classified phenol as an anesthetic/analgesic in Category I in a 0.5- to 1.5-percent concentration range and classified both phenol 0.5 to 1.5 percent and alcohol 70 percent in Category III as an antimicrobial in the mouth. The Oral Cavity Panel stated that commercially available mouthwashes contain ethanol as a solvent in concentrations up to 35 percent, but that concentrations above 35 percent cause burning of the mucous membranes (47 FR 22872). The Panel specifically stated that concentrations of ethanol that kill bacteria, e.g., 70 percent ethanol, cause burning and intense discomfort and are too irritating when applied to inflammations of the mucous membranes of the oral cavity (47 FR 22873). For the above reasons and because ethanol has marked potential for abuse, the Oral Cavity Panel recommended that the quantity of ethanol used as a solvent in pharmaceutical preparations should be limited to 35 percent.

In its report on OTC agents for the relief of oral discomfort (47 FR 22712 at 22737), the Dental Panel accepted the safety of 1.5 percent phenol in 70 percent ethanol for direct application to the gums for up to 7 days. The Panel concluded that up to 70 percent ethanol was an appropriate vehicle for 5 to 20 percent benzocaine with a maximum dosage of 1 milliliter and that the use of compound benzoin tincture (74 to 80 percent ethanol) and benzoin tincture (75 to 83 percent ethanol) was safe for occasional application to small areas of the oral mucosa regardless of the high alcohol content (47 FR 22747).

In its discussion of the effectiveness of ethanol as an antimicrobial agent (47 FR 22872), the Oral Cavity Panel pointed out that ethanol is ineffective as an antimicrobial ingredient at concentrations below 70 percent. However, that Panel also postulated that the lower concentrations of ethanol used as a solvent for an antimicrobial ingredient could act synergistically with the antimicrobial ingredient phenol, to produce an enhanced antimicrobial effect. The Panel then concluded that there were insufficient data from controlled studies to establish the effectiveness of ethanol alone as an antimicrobial agent and placed it in Category III.

In the advance notice of proposed rulemaking for OTC alcohol drug products for topical antimicrobial use published in the **Federal Register** of May 21, 1982 (47 FR 22324), the Miscellaneous External Panel stated that the "irritant action of alcohols is particularly marked on mucosa. The more concentrated the alcohol, the more pronounced are its irritant effects" (47 FR 22327). The Panel recommended caution in the topical use of 60 to 95 percent ethanol and 50 to 91.3 percent isopropyl alcohol on the mucous membranes (47 FR 22327) and placed the indication "For application to mucous membranes" in Category II (47 FR 22332).

In the tentative final monograph for OTC oral health care drug products (January 27, 1988; 53 FR 2436), the agency proposed Category I classifications for benzocaine and phenol as anesthetic/analgesic ingredients, and provided that benzocaine and phenol may be combined in an anesthetic/analgesic product. The tentative final monograph, however, did not address the use of phenol or alcohol as an antimicrobial because the agency intends to address the use of antimicrobials in the mouth in a future issue of the **Federal Register**.

Based on the historical usage of iodine as an active ingredient, the agency questions whether a total iodine concentration of 0.04 percent can be considered an inactive ingredient. A final determination on the status of iodine has not been made in any OTC drug rulemaking.

In the proposed rule concerning inactive ingredients (42 FR 19156 at 19157), the agency stated the following:

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

This proposal states that "flavors and flavoring adjuncts" are one of the

acceptable categories for inactive ingredients (42 FR 19160). The agency has no information that iodine is necessary as a flavor or flavoring adjunct, as defined in § 330.3(g) of the proposal, for use in OTC fever blister treatment drug products. The agency invites information and comments on (1) the use of iodine as a flavor or flavoring adjunct in OTC fever blister treatment and related drug products and (2) the minimum concentration of iodine needed to achieve a flavorant effect.

Notwithstanding the individual classifications of the active ingredients, the agency will require data to demonstrate safety and effectiveness of the combination of benzocaine, phenol, and alcohol (an anesthetic/analgesic and 2 antimicrobials (antiseptics) as described by the comment) on the oral mucosa for the temporary relief of cold sores and fever blisters. Therefore, the agency is classifying the combination of benzocaine, phenol, and alcohol in the above concentrations labeled for the treatment of cold sores and fever blisters in Category III.

References

1(1) OTC Volume 160278.

(2) Letter from M. H. Davis, Whitehall Laboratories, to W. E. Gilbertson, FDA, dated June 27, 1988, in OTC Volume 06FBETFM, Docket No. 78N-301F, Dockets Management Branch.

(3) Letter from M. H. Davis, Whitehall Laboratories, to W. E. Gilbertson, FDA, dated January 27, 1988, in OTC Volume 06FBETFM, Dockets No. 78N-301F, Docket Management Branch.

11. A manufacturer submitted information to the Miscellaneous External Panel on a medicated core lip balm product containing an inner core and outer base. The active ingredients in the inner core were allantoin 0.2 percent and camphor 0.1 percent. The active ingredients in the outer base were escalol 506 0.75 percent, menthol 0.1 percent, allantoin 0.2 percent, and benzocaine 0.1 percent. The product labeling contained the claims, "Instant relief of chapped, dry lips," [11] Relieves pain, helps heal * * * fever blisters, cold sores, sun or windburned lips" and "Eases discomfort of cold sores, fever bisters and cracked lips due to sun or windburn." The submission contained letters attesting to no growth of various microorganisms in in-vitro testing, literature references on some of the labeled ingredients, testimonial letters in support of efficacy, an unsubstantiated opinion by a chemical consultant that the product contains ingredients useful for the safe and effective treatment of lip skin dyscrasia, and information on the sales in units of the product over 5 years.

Section 348.20(b) of the tentative final monograph on OTC external analgesic drug products, published in the **Federal Register** of February 8, 1983 (48 FR 5852 at 5868), provides for the combination of camphor 0.1 to 3 percent as an analgesic, anesthetic, and antipruritic ingredient and allantoin 0.5 to 2 percent as a skin protectant ingredient. It also provides for the combination of benzocaine 5 to 20 percent and menthol 0.1 to 1 percent as analgesic, anesthetic, and antipruritic ingredients, and allantoin 0.5 to 2 percent as a skin protectant ingredient. However, the tentative final monograph does not provide for a combination product containing all of these ingredients, and it does not provide for a product containing an inner core with some ingredients and an outer base with other ingredients. Further, the allantoin is present at a concentration less than the 0.5 percent minimum concentration proposed in the skin protectant tentative final monograph. Allantoin at this subtherapeutic concentration is Category III. In addition, the benzocaine is also present at a concentration less than the 5 to 20 percent minimum concentration proposed in the external analgesic tentative final monograph and thus is also Category III. Any Category III ingredients in a combination containing Category I ingredients render the combination Category III. Finally, there are no data showing how this inner core and outer base work, or on the need for different analgesic, anesthetic, and antipruritic ingredients in each area of the product. The agency is also aware that this product is no longer marketed (Ref. 1).

Escalol 506 is synonymous with padimate A, a Category I sunscreen ingredient at 1 to 5 percent. The submitted product contained 0.75 percent escalol 506, which would make it Category III. Combinations of sunscreen and external analgesic ingredients are discussed in comment 5 above.

The agency considers the claim "helps heal fever blisters and cold sores" to be a Category III skin protectant claim for wound healing agents based on the Topical Analgesic Panel's finding that no controlled studies have conclusively documented that skin protectant ingredients aid in wound healing (see 43 FR 34628 at 34647; August 4, 1978). The information submitted by the manufacturer did not include any safety and effectiveness data supportive of the use of the product for its labeled indications. In the absence of other in-vivo safety data, the letters attesting to no growth of various microorganisms in in-vitro testing are insufficient to demonstrate the product's safety. Further, testimonial letters are not adequate to establish either product or ingredient effectiveness. Isolated reports, lacking details which permit objective scientific evaluation, cannot serve as the basis for establishing effectiveness. (See 21 CFR 330.10(a)(4)(ii).) The agency is therefore classifying the combination product as Category III, due to a lack of adequate data to establish safety and effectiveness.

Reference

(1) Memorandum of telephone conversations, June 9, 1988 and July 26, 1988, between H. Gordon, Commerce Drug, Inc., and M.T. Benson, FDA, in OTC Volume 06FBETFM, Docket No. 78N-301F, Dockets Management Branch.

12. One manufacturer submitted data to the Miscellaneous External Panel on a product containing a combination of 4 percent spirits of ammonia, 0.27 percent aqua ammonia, 0.4 percent phenol (90 percent), and 1 percent camphor in an ointment base and having the claim "quick relief for cold sores, fever blisters * * *" among other claims (Ref. 1). The submission included: (1) Acute oral toxicity studies, using the product on albino rats, in which the tester concluded that the product is nontoxic; (2) eye irritation study, on albino rabbits, in which the tester concluded that the product is not classified as an eye irritant in accordance with the Federal Hazardous Substances Act of September 17, 1964; and (3) a repeated insult patch test study, on 66 human subjects, in which the tester concluded that the product was nonirritating to any subject and showed no sensitization. The manufacturer indicated that sales exceeded 20,000,000 units in a 2-year period with no more than three complaints of an apparent allergic reaction. In support of efficacy, the manufacturer submitted a number of personal testimonials from several physicians and a number of consumers. The manufacturer contended that the long history and experience of the product may be considered substantiation in lieu of extensive scientific studies.

The Topical Analgesic Panel recommended that combination products containing Category I external analgesic active ingredients (topical analgesics/anesthetics/antipruritics) which depress cutaneous sensory receptors (e.g., camphor, phenol) combined with any Category I external analgesic (counterirritant) which stimulates cutaneous sensory receptors (e.g., strong ammonia water) be

classified as Category II because of the opposing pharmacological actions of each class (44 FR 69768 at 69787).

Likewise, the agency did not allow such combinations of ingredients in the tentative final monograph for OTC external analgesic drug products (48 FR 5852). The agency notes also that the phenol concentration of 0.4 percent in the combination product is below the range of 0.5 to 1.5 percent proposed as safe and effective in the external analgesic tentative final monograph (48 FR 5852 at 5867).

With respect to the personal testimonials and extensive marketing history mentioned by the comment, these items alone cannot be regarded as adequate proof of safety of effectiveness without the corroboration of scientific data. Agency regulations provide that human experience during marketing may be used to support safety and to corroborate clinical effectiveness investigations but that isolated case reports, random experience reports, and reports lacking the details which permit scientific evaluation are not considered in establishing effectiveness. (See 21 CFR 330.10(a)(4) (i) and (ii).) The agency notes that the manufacturer did not provide any effectiveness data for its product. Based on this fact and the Topical Analgesic Panel's recommendations discussed above, the agency is classifying this combination product in Category II.

Reference

(1) OTC Volume 160096.

13. One manufacturer submitted information to the Miscellaneous External Panel on a product containing 745.2 milligrams (mg) pectin per fluid ounce (oz) (approximately 2.5 percent) and 486 mg bismuth sodium tartrate per fluid oz (approximately 1.6 percent) and labeled for temporary relief of discomfort due to cold sores, fever blisters, and chapped lips (Ref. 1). The submission did not contain any data on the safety or effectiveness of the active ingredients. The manufacturer contended that the safety of the active ingredients has been well-documented in the literature and standard pharmacology texts. However, no citations were provided. Regarding effectiveness, the manufacturer stated that the bismuth salt has an astringent effect and may exert a mild antiseptic effect and thus prevent secondary infection, although no antimicrobial claims are made for the product. The manufacturer added that the bismuth salt also forms a smooth, protective coating which helps to keep the lesions dry, and the pectin in the product acts as a demulcent. The manufacturer stated that the product is not a cure for cold sores and fever blisters, but it relieves discomfort, reduces irritation, and helps the self-healing process. The manufacturer concluded that safety has been substantiated by a long history of use without reports of adverse effects and no complaints that the product was ineffective.

As noted, the comment did not submit data on safety and effectiveness, and the agency has insufficient information to classify the ingredients bismuth sodium tartrate and pectin in Category I for relief of discomfort due to cold sores and fever blisters. Regarding safety, the agency takes cognizance of the manufacturer's statement that an average application of the product contains less than 2 mg of bismuth sodium tartrate and about 2.5 mg pectin, and that these amounts are far less than those ingested in antacid and antidiarrheal drug products. While some bismuth salts are included in the antacid monograph, bismuth sodium tartrate is not one of them. Further, no bismuth salts are currently classified in Category I as an antidiarrheal.

The agency notes that the Miscellaneous Internal Panel, in its report on OTC digestive aid drug products (January 5, 1982; 47 FR 454), reviewed the ingredient bismuth sodium tartrate and cited reports of bismuth encephalopathy from oral and topical use of products containing bismuth salts, including the pectate salt. The Panel reported that the implication is that the bismuth portion of the compound is toxic to the nervous system, although the mechanism involved is not clear. Based on that report, the agency has several safety concerns: (1) The bismuth sodium tartrate could react with pectin to form bismuth pectate, an implicated salt in causing bismuth encephalopathy, and (2) the product might be applied to sores on the mucous membrane, and thus provide for entry of the bismuth salt into the systemic circulation. Data are needed to show that these problems would not occur.

Regarding effectiveness, no clinical data were submitted to support any of the product's labeling claims. Clinical data are needed to demonstrate the effectiveness of the combination product and to show that each ingredient contributes to the claimed effects. In the absence of adequate safety and effectiveness data, the agency classifies the individual ingredients and the combination of bismuth sodium tartrate and pectin in Category III.

Reference

(1) OTC Volume 160197.

14. The agency has evaluated all of the external analgesic active ingredients and combinations of active ingredients that were proposed as Category I in the tentative final monograph for OTC external analgesic drug products that was published in the **Federal Register** on February 8, 1983 (48 FR 5852 at 5867 to 5868) to determine which ones would be amenable to use for relieving the pain and itching of fever blisters and cold sores. The agency has determined that any of the ingredients listed in proposed § 348.10 (a) and (b) that depress cutaneous sensory receptors would be appropriate to use because of their analgesic, anesthetic, and antipruritic effects in relieving pain and itching of fever blisters and cold sores. These ingredients are classified in the tentative final monograph in § 348.10(a) as the "amine and caine"-type local anesthetics and in § 348.10(b) as the alcohols and ketones. However, the agency does not consider the Category I external analgesic antihistamine or hydrocortisone active ingredients in proposed § 348.10 (c) and (d) as appropriate for use on fever blisters or cold sores.

The agency has no basis to conclude that the action of an antihistamine in nullifying the effects of released histamine would relieve pain and itching of fever blister or cold sore lesions. In addition, no data have been submitted on products containing antihistamine ingredients for topical use for the treatment of fever blisters or cold sores, and the agency is not aware of such products historically being used for this purpose. Data are needed to demonstrate the safety and effectiveness of antihistamine ingredients for this topical use.

In the advance notice of proposed rulemaking for OTC external analgesic drug products, the Topical Analgesic Panel reviewed hydrocortisone preparations extensively but made no mention of the use of this ingredient on fever blisters or cold sores (44 FR 69768 at 69813 to 69824; December 4, 1979). The agency's current class labeling guideline for topical corticosteroids does not include the use of hydrocortisone on fever blisters or cold sores (Ref. 1). These guidelines state that topical corticosteroids are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Fever blisters and cold sores are not considered steroid-responsive dermatoses. The agency notes that the Miscellaneous External Panel, in its statement on OTC drug products for the treatment of fever blisters (47 FR 39412 at 39420), cited a

reference (Ref. 2) which stated that steroid hormone ointments are not recommended because they lessen defenses against infections and may spread the virus. The agency further notes that conflicting results have been reported when hydrocortisone was used against herpes. Ratner (Ref. 3) states that corticoids have not been found useful for treatment of *herpes simplex*. Robinson, Robinson, and Strahan (Ref. 4) state that subjects with *herpes simplex* did not show any response to treatment with hydrocortisone. Mullins and Hicks (Ref. 5) state that three cases of *herpes simplex* responded favorably to hydrocortisone within 24 hours. However, the concentration of the hydrocortisone acetate used was 2.5 percent, which is not an OTC concentration. Polano (Ref. 6) rated treatment with 1 percent hydrocortisone of one subject having *herpes simplex* as moderate. The agency finds these data too limited to establish that hydrocortisone is useful in treating fever blisters or cold sores. In addition, the agency is not aware of products containing hydrocortisone historically being used for this purpose. The agency concludes that additional data are needed to demonstrate the safety and effectiveness of hydrocortisone for this topical use.

The agency does not consider any of the counterirritant active ingredients proposed in § 348.12 as appropriate for use on fever blisters and cold sores because those ingredients stimulate rather than depress cutaneous sensory receptors. Thus, the mechanism of action of these ingredients is not desired for relief of pain or itch of fever blisters or cold sores.

Based on the above, the agency is proposing that the following ingredients be classified as Category I for use in relieving the pain and itching of fever blisters and cold sores at the following concentrations: Under § 348.10(a): (1) Benzocaine 5 to 20 percent, (2) butamben picrate 1 percent, (3) dibucaine 0.25 to 1 percent, (4) dibucaine hydrochloride 0.25 to 1 percent, (5) dimethisoquin hydrochloride 0.3 to 0.5 percent, (6) dyclonine hydrochloride 0.5 to 1 percent, (7) lidocaine 0.5 to 4 percent, (8) lidocaine hydrochloride 0.5 to 4 percent, (9) pramoxine hydrochloride 0.5 to 1 percent, (10) tetracaine 1 to 2 percent, and (11) tetracaine hydrochloride 1 to 2 percent. Under § 348.10(b): (1) Benzyl alcohol 10 to 33 percent, (2) camphor 0.1 to 3 percent, (3) camphor 3 to 10.8 percent when combined with phenol 4.7 percent, (4) camphorated metacresol (camphor 3 to 10.8 percent and metacresol 1 to 3.6 percent), (5) juniper tar 1 to 5 percent, (6) menthol 0.1 to 1 percent, (7) phenol 0.5 to 1.5 percent, (8) phenol 4.7 percent when combined with camphor in accordance with § 348.20(a)(4), (9) phenolate sodium 0.5 to 1.5 percent, and (10) resorcinol 0.5 to 3 percent.

Based on the above individual active ingredients being acceptable for this use, the agency is also proposing that the following combinations of external analgesic ingredients, with or without active ingredients from other classes, are appropriate for use in relieving pain and itching of fever blisters and cold sores:

(1) Any ingredient identified in § 348.10(a) combined with any ingredient identified in § 348.10(b),

(2) Any ingredient identified in § 348.10(b) (1), (5), (7), (9), and (10) combined with camphor and menthol identified in § 348.10(b) (2) and (6),

(3) Camphor and phenol identified in § 348.10(b) (3) and (8) combined in a light mineral oil, U.S.P. vehicle,

(4) Any ingredient identified in § 348.10 (a) or (b) or any combination identified in § 348.20(a) (1) or (3) combined with any generally recognized safe and effective skin protectant active ingredient or skin protectant combination identified in part 347 for treatment of fever blisters and cold sores provided the product is labeled for the concurrent symptoms.

References

(1) Topical Corticosteroids Class Labeling Guideline, Food and Drug Administration in OTC Volume 06FBETFM, Docket No. 78N-301F, Dockets Management Branch.

(2) "Canker Sores and Fever Blisters," National Institute of Dental Research, DHEW Publications No. [NIH] 79-247.

(3) Ratner, H., "The Status of Corticosteroid Therapy in Dermatology," *California Medicine*, 83:331-335, 1955.

(4) Robinson, Jr., H.M., R.C.V. Robinson, and J.F. Strahan, "Indications for Local Hydrocortisone Therapy," *Medical Times*, 83:227-237, 1955.

(5) Mullins, J.F., and J.H. Hicks, "Hydrocortisone Ointment in the Treatment of Dermatologic Disorders," *Texas State Journal of Medicine*, 50:703-705, 1954.

(6) Polano, M.K., "On the External Use of Hydrocortisone in Skin Diseases," *Acta Dermato-Venereologica*, 36:283-290, 1956.

(7) Russell, B., et al., "A Valuation of Hydrocortisone Ointment," *The Lancet*, 268:1038-1043, 1955.

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.* The discussion below only applies to external analgesic drug products used for the treatment of fever blisters and cold sores. Skin protectant drug products used for the treatment of symptoms of fever blisters and cold sores are discussed in the skin protectant rulemaking published elsewhere in this issue of the Federal Register.

Although the Miscellaneous External Panel mentioned the use of external analgessic ingredients for the treatment of fever blisters, it did not review or classify 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 statement on OTC drug products for the treatment of fever blisters (47 FR 39412 at 39420). The Panel noted at 47 FR 39418 that many of these ingredients labeled with claims as external analgesic drug products for treatment of fever blisters have been previously addressed by other OTC advisory review panels. The agency is aware that many of these products were reviewed by the Topical Analgesic Panel.

The agency has further considered the Topical Analgesic Panel's recommendations 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 on tannic acid (see comment 2 above) and zinc sulfate (see comment 1 above.

Based upon the above discussion, the agency is adding two astringent active ingredients to the "Summary of Ingredient Categories" table for external analgesic active ingredients that appeared in the tentative final monograph for OTC external analgesic drug products (48 FR 5852). These additions involve ingredients used for the treatment of fever blisters and cold sores, i.e., tannic acid and zinc sulfate. An updated table appears below for the convenience of the reader.

SUMMARY OF INGREDIENT CATEGORIES

External analgesic active ingredients	Category
Analgesic, anesthetic, antipruritic active ingredients:	
Aspirin	III
Benzocaine	I
Benzyl alcohol	I
Butamben picrate	I
Camphor	I
Camphorated metacresol	II
Chloral hydrate	III
Chlorobutanol	III
Cyclomethycaine sulfate	I
Dibucaine	I
Dibucaine hydrochloride	I
Dimethisoquin hydrochloride	I

SUMMARY OF INGREDIENT CATEGORIES—Continued

External analgesic active ingredients	Category
Diphenhydramine hydrochloride	I
Dyclonine hydrochloride	I
Eugenol	III
Glycol salicylate	III
Hexylresorcinol	III
Hydrocortisone [1]	III
Hydrocortisone acetate [1]	III
Juniper tar	I
Lidocaine	I
Lidocaine hydrochloride	I
Menthol	I
Methapyrilene hydrochloride	II
Phenol	I
Phenolate sodium	I
Pramoxine hydrochloride	I
Resorcinol	I
Salicylamide	III
Tetracaine	I
Tetracaine hydrochloride	II
Thymol	III
Trolamine salicylate [2]	III
Tripelennamine hydrochloride	III
Counterirritant ingredients:	
Allyl isothiocyanate	III
Strong ammonia solution [3]	III
Camphor	III
Capsaicin	III
Capsicum	III
Capsicum oleoresin	III
Chloral hydrate	III
Eucalyptus oil	III
Histamine dihydrochloride	III
Menthol	III
Methyl nicotinate	III
Methyl salicylate	III
Turpentine oil	III
Astringent ingredients:	
Tannic acid	III
Zinc sulfate	III
Other ingredients:	
Bismuth sodium tartrate	III
Pectin	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.
[3] Identified by the Topical Analgesic Panel as ammonia water, stronger.

In its statement, the Miscellaneous External Panel also listed a number of other ingredients that it said should be considered in other appropriate rulemakings for their use in treating fever blisters and cold sores, and their related symptoms (47 FR 39412 at 39418). The Panel recommended that the ingredients allantoin, glycerin, petrolatum, tannic acid, and white petrolatum for use on fever blisters be referred to the rulemaking on skin protectant ingredients and that other ingredients be referred to rulemakings which FDA considers appropriate. The agency notes that many of the ingredients listed by the Panel were intended as inactive ingredients, and they need not be reviewed as external analgesics for use on fever blisters. They are: ammonium carbonate, aromatic oily solution, beeswax, BHA, candelilia wax, carnauba wax, castor oil, cetyl alcohol, lanolin, lanolin alcohol, mineral oil, octyldodecanol, ozokerite, paraffin, peppermint oil, petrolatum propyl *p*-benzoate, sorbitan sesquioleate, soya sterol, spermaceti, titanium dioxide, wheat germ glycerides, and white petrolatum. One ingredient was listed under three names and was submitted as active and inactive, i.e., Escalol 506, amyl dimethyl *p*-aminobenzoate, and amyl para-dimethylaminobenzoate. That ingredient is also known as padimate-A, a Category I sunscreen ingredient, which together with homosalate has been deferred to the sunscreen rulemaking. Alcohol, calcium silicate, and talcum power were not submitted to the Panel, although alcohol is being deferred to the rulemaking on OTC first-aid antiseptic drug products for use on cuts and wounds. Benzalkonium chloride is also being deferred to that rulemaking. Pyridoxine hydrochloride was deferred to the rulemaking on OTC skin protectant drug products. The following active ingredients have been considered in this rulemaking: ammonia, benzocaine, bismuth sodium tartrate, camphor, menthol, pectin, and phenol. The following ingredients were deferred to the oral cavity drug products rulemaking: anhydrous glycerol and carbamide peroxide.

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 ingredient or conditions included in the review for the treatment of fever blisters and cold sores, 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 the comments and other relevant information and concludes that it will tentatively adopt the substance of the Miscellaneous External Panel's statements, including the Panel's description of what "fever blisters" and "cold sores" are. This Panel did not recommend a specific monograph for external analgesic drug products for use in the treatment of fever blisters and cold sores. 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). The agency is amending that proposed monograph to include conditions for the treatment of fever blisters and cold sores 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 adding a definition for "fever blister, cold sore" in proposed § 348.3(h) as follows: "A vesicle that occurs at the junction of the mucous membrane and skin on the lips or nose and is caused by the virus *herpes simplex*, type 1."

2. The agency is proposing to add new paragraph (a)(4) to § 348.50 as an appropriate alternative statement of identity for external analgesic drug products used for the treatment of cold sores or fever blisters to read as follows: (4) *For products containing any ingredient in § 348.10 (a) or (b).* "Fever blister/cold sore treatment." The agency considers this proposed statement of identity to be descriptive and informative to consumers.

3. The agency is proposing to add new paragraph (b)(5) to read as follows:

(5) *For products containing any external analgesic active ingredients identified in § 348.10 (a) and (b).* "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: "fever blisters," "cold sores," or "fever blisters and cold sores.")) (See comment 3 above.)

4. The agency is proposing that all of the active ingredients included in § 348.10 (a) and (b) of the tentative final monograph for OTC external analgesic drug products be classified as Category I for use in relieving the pain and itching of fever blisters and cold sores. (See comment 14 above.)

5. The agency is classifying zinc sulfate in Category III as an external analgesic for the treatment of fever blisters and cold sores. (See comment 1 above.)

6. The agency is classifying tannic acid in Category III as an external analgesic for the treatment of fever blisters and cold sores. (See comment 2 above.)

7. The agency is proposing that certain combinations of external analgesic ingredients, with or without active

ingredients from other classes, are appropriate for use in relieving the pain and itching of fever blisters and cold sores. (See comment 14 above.) The agency is adding a corresponding section for the labeling of such combination products.

8. The Agency is classifying the combination of an external analgesic and a sunscreen in Category III. (See comment 5 above.)

9. The agency is classifying the combination of an external analgesic, antimicrobial, and astringent in Category III. (See comment 6 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 no one of these rules, including this proposed rule for OTC external analgesic drug products for the treatment of fever blisters and cold sores, 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). The 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 for fever blisters and cold sores 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 exernal 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 May 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 May 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 May 31, 1990 publication in the **Federal Register.** 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 January 31, 1991, 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 April 1, 1991. 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 April 1, 1991. 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, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

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

§ 348.3 Definitions.

* * * * *

(h) *Fever blister, cold sore.* A vesicle that occurs at the junction of the mucous membrane and skin on the lips or nose and is caused by the virus *herpes simplex,* type 1.

3. Section 348.20 is amended by adding new paragraph (b)(3) to read as follows:

§ 348.20 Permitted combinations of active ingredients.

* * * * *

(b) * * *

(3) Any ingredient indentified in § 348.10 (a) or (b) or any combination identified in § 348.20(a) (1) or (3) may be combined with any generally recognized safe and effective skin protectant active ingredient or skin protectant combination identified in part 347 of this chapter for treatment of fever blisters and cold sores provided the product is labeled according to § 348.52.

4. Section 348.50 is amended by adding new paragraph (a)(4), by redesignating paragraph (b)(5) as paragraph (b)(6), and by adding new paragraph (b)(5) to read as follows:

§ 348.50 Labeling of external analgesic drug products.

(a) * * *

(4) *For products containing any ingredient in § 348.10 (a) or (b).* "Fever blister/cold sore treatment."

(b) * * *

(5) *For products containing any external analgesic active ingredients*

identified in § 348.10 (a) and (b). "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: "fever blisters," "cold sores," or "fever blisters and cold sores")).

* * * * *

5. Section 348.52 is added to read as follows:

§ 348.52 Labeling of permitted combinations.

Statements of identity, indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable.

(a) *Statement of identity.* For a combination drug product that has an established name, the labeling of the product states the established name of the combination drug product, followed by the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC drug monographs. For a combination drug product that does not have an established name, the labeling of the product states the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC drug monographs.

(b) *Indications.* The labeling of the product states, under the heading "Indications," the indication(s) for each ingredient in the combination, as established in the indications sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph (b). Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in the applicable OTC drug monographs, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(c) *Warnings.* The labeling of the product states, under the heading "Warnings," the warning(s) for each ingredient in the combination, as established in the warnings sections of the applicable OTC drug monographs.

(d) *Directions.* The labeling of the product states, under the heading "Directions," directions that conform to the directions established for each ingredient in the directions sections of the applicable OTC drug monographs. When the time intervals or age limitations for administration of the individual ingredients differ, the directions for the combination product may not exceed any maximum dosage limits established for the individual ingredients in the applicable OTC drug monograph.

Dated: December 25, 1989.

James S. Benson,

Acting Commissioner of Food and Drugs.

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