DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 348

[Docket No. 78N-0301]

External Analgesic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) external analgesic drug products are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products and public comments on an advance notice or proposed rulemaking that was based on those recommendations. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or request for oral hearing before the Commissioner of Food and Drugs on the proposed regulation by April 11, 1983. New data by February 8, 1984. Comments on the new data by April 9, 1984. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Written comments on the agency's economic impact determination by June 8, 1983.

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

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

SUPPLEMENTARY INFORMATION: In the **Federal Register** of December 4, 1979 (44 FR 69768) FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC external analgesic drug products, together with the recommendations of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by March 6, 1980. Reply comments in response to comments filed in the initial comment period could be submitted by April 3, 1980.

In a notice published in the **Federal Register** of September 26, 1980 (45 FR 63878), the agency advised that it had reopened the administrative record for OTC external analgesic drug products to allow for consideration of recommendations on camphor-containing drug products that had been received from the Advisory Review Panel on OTC Miscellaneous External Drug Products after the date the administrative record previously had officially closed. The agency concluded that the Miscellaneous External Panel's recommendations should be available to the agency in developing a proposed regulation on external analgesic drug products in the form of a tentative final monograph.

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

The advance notice of proposed rulemaking, which was published in the **Federal Register** on December 4, 1979 (44 FR 69768), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the present document is designated in the OTC drug review regulations as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule), FDA states for the first time its position on the establishment of a monograph for OTC external analgesic drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC external analgesic drug products.

In response to the advance notice of proposed rulemaking, 1 trade association, 10 drug manufacturers, 36 health professionals, and 4 consumers submitted comments. In response to the notice of reopening the administrative record to allow for consideration of recommendations on camphor-containing drug products, one trade association, six drug manufacturers, and one drug marketer submitted comments. Copies of the comments received are also on public display in the Dockets Management Branch.

This proposal to establish Part 348 (21 CFR 348) constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC external analgesic drug products as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them.

FDA published in the **Federal Register** of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established.

Accordingly, this provision is now deleted from the regulations. The regulations now provide that any testing necessary to resolve the safety and effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process, before the establishment of a final monograph (46 FR 47738).

Although it was not required to do so under *Cutler*, FDA will no longer use the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III 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 products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved new drug application. Further, any OTC drug products subject to this monograph that are repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In the advance notice of proposed rulemaking for OTC external analgesic drug products (published in the **Federal Register** of December 4, 1979 (44 FR 69768)), the agency suggested that the conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the **Federal Register** and that the conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of whether further testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

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

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss, but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the **Federal Register**. The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and have their products in compliance in the marketplace. However, if the agency determines that any labeling for a condition included in the final monograph should be implemented sooner, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular 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 notice published in the **Federal Register** of July 21, 1972 (37 FR 14633) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

In the **Federal Register** of September 7, 1982 (47 FR 39412), FDA issued a notice of reopening of the administrative record for OTC external analgesic drug products to allow for consideration of the Miscellaneous External Panel's recommendations on external analgesic drug products used for the treatment of diaper rash, for prevention of poison ivy, oak, and sumac, for the treatment of fever blisters, as male genital desensitizers, as astringents, and as insect bite neutralizers. The agency will address the use of external analgesic active ingredients for these uses in this rulemaking in a future issue of the **Federal Register**.

I. The Agency's Tentative Conclusions on the Comments

A. General Comments on External Analgesic Drug Products

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

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

2. One comment stated that two products, both containing the active ingredients camphor, menthol, eugenol, and eucalyptus oil, had "grandfathered" status under section 201(p)(1) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)(I)). The comment pointed out that, although these products do not comply with the Panel's recommended monograph because of their high level of camphor, they have been continuously marketed since 1923. The comment argued that, because of the grandfather status, the conclusions of the OTC drug review should not be applicable to these products.

The agency points out that after this comment was submitted the two products were reformulated to reduce the concentration of camphor from 25 percent to 11 percent, in conformance with the Panel's recommendations.. Consequently, the question of grandfather status for those 25 percent products is moot.

The "grandfather" clause in the act of 1938 is not applicable to any drug relabeled or reformulated after June 25, 1938. Similarly, a drug marketed before the 1962 amendments to the act, which was not then a new drug or covered by a new drug application, is subject to the provisions of these amendments regarding effectiveness if the drug has been reformulated or relabeled. The 1938 and 1962 grandfather clauses apply only to the new drug provisions of the act and not to the adulteration or misbranding provisions. The OTC drug review was designed to implement both the misbranding and the new drug provisions of the act. Therefore, the grandfather clauses do not preclude the agency from reviewing any currently marketed OTC drug, regardless of whether it has grandfather protection from the new drug provisions, in order to ensure that the drug is not misbranded.

B. Comments on External Analgesic Ingredients

3. A number of comments expressed opinions on the Panel's recommended switch of hydrocortisone to OTC marketing status. The comments that favored OTC marketing pointed out the long history of experience with this drug as well as the savings to the consumer from OTC availability. Several comments stated that the recommended OTC indications would permit informed and prudent use of hydrocortisone products by providing consumers with appropriate examples of self-diagnosable conditions for which hydrocortisone products provide appropriate therapy. Opposing comments stated that hydrocortisone is likely to be used inappropriately because the average consumer is unable to distinguish between a simple rash and such skin conditions as herpes simplex, scabies, seborrheic dermatoses, and tinea cruris (jock itch). The comments added that inappropriate treatment and delay in diagnosis might cause the conditions to spread or become worse at considerable cost to the consumer.

The agency agrees with the Panel that the OTC marketing of hydrocortisone is of significant benefit to consumers because it provides them with an effective drug for self-treatment of certain minor skin irritations. The indications for OTC use are for self-limiting, self-diagnosable conditions. The warning proposed in § 348.50(c)(1)(iii) of this tentative final monograph, "If condition worsens, or if symptoms persist for more than 7 days or clear up and occur again within a few days, discontinue use of this product and consult a" (select one of the following: "physician" or "doctor,") is intended to prevent unlimited consumer use of these products for serious conditions that require professional treatment. (See comment 27 below.) The agency tentatively concludes that hydrocortisone is safe and effective for its labeled OTC uses and that the benefits of OTC availability outweigh any potential misuse that may occur.

4. Two comments form the same source requested that the maximum allowable concentration of camphor recommended by the Panel in §348.10 (a)(3) be raised from 11 to 25 percent. The comments cited a study to determine the dermal irritancy and possible toxicity of 25 percent camphor and argued that the results of the study justify this higher concentration (Ref. 1). The comments also cited the long marketing history of a product containing a higher concentration of camphor with no reports of major problems.

The agency disagrees with the comments. The study submitted by one comment to justify raising the camphor limit to 25 percent used traditional Draize procedures in which a product containing 25 percent camphor was applied to rabbits' skin for 21 consecutive days (Ref. 1). This is a standard method of testing topical irritancy. The Panel stated that camphor in concentrations above 11 percent is not harmful when used topically, but the Panel was concerned about poisoning if products containing higher concentrations were accidentally ingested (44 FR 69803). Eleven percent was chosen as a maximum limit by the Panel because higher concentrations are not any more effective as counterirritants, but can cause more serious adverse reactions if accidentally ingested. The agency concurs with the Panel's conclusion.

Furthermore, the product discussed in the comment has been reformulated, lowering the camphor concentration from 25 percent to 11 percent (Ref. 2). The agency is not aware of counterirritant products containing more than 11 percent camphor now on the OTC market; therefore, the agency finds no reason to consider camphor concentrations greater than 11 percent any further in this document.

References

(1) Comment No. C00027, Docket No. 78N-0301, Dockets Management Branch.

(2) Food and Drug Administration, "Drug Product Listing for Tiger Balm Ointment," Haw Par Brothers International Limited, January 15, 1980 and January 9, 1981, included in OTC Volume 06BTFM.

5. A number of comments objected to the recommendations of the Miscellaneous External Panel, included in the rulemaking for external analgesic drug products on September 26, 1980 (45 FR 63878), that the quantity of camphor in OTC drug products be limited to 2.5 percent, that no package contain more than 360 milligrams (mg) of camphor, and that safety packaging be used. One comment argued that it is unacceptable to limit household drug products to 360 mg of camphor per container, which would be the equivalent of a spoonful-size container for many products, on the basis that accidental ingestion of larger amounts may cause toxic effects. Another comment argued that the Miscellaneous External Panel was wrong in basing its calculation of the toxic dose of 30 milligrams/kilogram (mg/kg) on a single report of death following ingestion by a 150-pound man of 2 grams (g) of camphor. The comment argued that other reports place the toxic dose higher than 30 mg/kg and that most of the reported cases of camphor poisoning may not be true poisonings with toxic signs and symptoms. The comment added that of 542 cases of camphor poisoning cited by the Poison Control Center for 1974, only 101 reported any symptoms, and of this number only 77 were hospitalized. Several comments pointed out that there are no reported fatalities associated with products containing 11 percent or less camphor, and that most of the poisonings described by the Miscellaneous External Panel were due to ingestion of camphorated oil, which contains 20 percent camphor in oil. One comment pointed out that limiting the package size to avoid potential misuse would be a proper consideration for the Consumer Product Safety Commission under the provisions of the Poison Prevention Packaging Act, and should not be incorporated into an OTC drug monograph. Another comment argued that there was no justification for applying the recommendations of the Miscellaneous External Panel to nonliquid formulations of camphor because of the lower risk of ingestion of these formulations.

The agency notes that the Topical Analgesic Panel considered various comments, reports, and editorials submitted to it concerning the toxicity and frequency of poisonings from camphor-containing preparations, particularly in children because that population has the highest incidence of such toxicity. The Panel concluded that the cases of accidental ingestion of products containing 11 percent or less camphor by children rarely resulted in severe adverse reactions and that current regulations and labeling requirements are adequate. The agency has reviewed both panels' recommendations and the adverse reaction reports for products containing camphor and concludes that, at this time, there is no need to limit camphor content to 360 mg per package for products covered by this tentative final monograph. The camphor concentration is being limited to 11 percent or lower as recommended by the Topical Analgesic Panel. (See comment number 4 above.) A final rule declaring camphorated oil products to be new drugs and misbranded was published in the **Federal Register** of September 21, 1982 (47 FR 41716).

There are few reports of adverse reactions from ingestion of solid dosage forms containing camphor; however, the agency believes that safety packaging of liquid products would reduce the risk

that children might ingest these products. The agency strongly recommends that manufacturers voluntarily package such products in child-resistant containers. In addition, these products must bear the warning: "For external use only." The agency recommends that manufacturers voluntarily print this warning in a larger size print and/or in a different color from other information on the lable to draw consumers' attention to it. The agency believes that if manufacturers take these additional steps, the number of accidental ingestions can be reduced.

6. One comment requested clarification of the gap between the dosage ranges for menthol as an analgesic, anesthetic, or antipruritic (0.1 to 1.0 percent) and as a counterirritant (1.25 to 16 percent).

The Panel proposed two dosage ranges to emphasize the distinction between the two different OTC uses of menthol and the different labeling associated with each use. The agency concurs with the Panel's recommendations of these dosage ranges.

7. Two comments submitted data on the effectiveness of trolamine salicylate (formerly triethanolamine salicylate) as a topical analgesic. Based on these data, one of the comments suggested that the monograph include a class of external analgesics that "act upon painful structures below the skin by absorption of the active ingredient directly into subcutaneous structures" and that trolamine salicylate be placed in this class. The comment also suggested the following indications for this class: "For the temporary relief of minor aches and pains of muscles and joints. Also as a topical adjunct for pain due to arthritis and rheumatism." Both comments requested that trolamine salicylate be placed in Category I basd on the data submitted.

The agency has reviewed the data submitted and concludes that they are not sufficient to support general recognition of effectiveness for trolamine salicylate as an OTC external analgesic.

The studies by Ehrlich (Ref. 1), Charles (Ref. 2), Brown (Ref. 3), and Roth (Ref. 4) were randomized, double-blind, crossover evaluations of 10 percent trolamine cream versus placebo. None of these studies reported any significant differences between active drug and placebo for any of the measurements recorded.

A double-blind, placebo-controlled, crossover study by Batterman and Sanders (Ref. 5) evaluated the effect of 10 percent trolamine salicylate in relieving the pain of arthritis of the hand in two groups of patients. In one group there was subjective evidence only of superiority of the trolamine cream over placebo, whereas measurable indicators such as hand-grip strength and finger-joint circumference showed no statistically significant improvement. In the other group, trolamine salicylate showed no superiority over the placebo in any of the three measurable criteria. Thus, the results of this study do not indicate any clear superiority of trolamine salicylate over placebo.

Golden (Ref. 6) compared topically applied 10 percent trolamine salicylate cream to oral aspirin in a double-blind parallel study of the relief of rheumatic pain, concluding that the topically applied trolamine salicylate was at least as effective as aspirin in providing pain relief. However, the study design has several deficiencies. History of aspirin use, effective dose, and adverse reactions were not recorded for each subject. Without this information about aspirin response, there is a potential for bias against aspirin in treatment response and adverse reactions.

Altschuler and Golden (Ref. 7) studied 10 percent trolamine salicylate cream in patients with musculoskeletal pain. Of the six results reported, only one was statistically significant. Furthermore, the selective reporting of these six results renders this report uninformative, and no conclusions can be made concerning the effectiveness of trolamine salicylate.

Patel and Chappelle (Ref. 8) reported results observed from unblinded and uncontrolled clinical trials of trolamine salicylate in two French hospitals. The results cannot be assessed because of the lack of a control group.

The comments also included information on the penetrating properties of trolamine salicylate, including in vivo studies in animals, a boiled-egg technique said to demonstrate penetration through protein, and a cup method to demonstrate penetration through muscle and connective tissue. This information is not adequate or suitable to demonstrate effectiveness of trolamine salicylate as a topical analgesic.

Because the submitted information fails to demonstrate that this ingredient would be effective for application at the site of pain or for any use as an external analgesic, the agency does not agree with the comments that trolamine salicylate should be placed in a new class of external analgesic drug products. Trolamine salicylate remains in Category III as an anesthetic, analgesic, and antipruritic in this tentative final monograph. The agency's detailed review and evaluation of the studies submitted are on file in the Dockets Management Branch (Refs. 9 and 10). In response to the agency's review, a comment submitted additional data on trolamine salicylate (Ref. 11). These data were submitted after the administrative record had closed and will be addressed after publication of this tentative final monograph.

References

(1) Ehrlich, G. E., "Myoflex Creme in Patients with Chronic Musculoskeletal Complaints," Comment No. C0008, Docket No. 78N-0301, Dockets Management Branch.

(2) Charles, A. A., "Myoflex Creme in the Treatment of Chronic Musculoskeletal Complaints," Comment No. C0008, Docket No. 78N-0301, Docket Management Branch.

(3) Brown, B., "Myoflex/Chronic Musculoskeletal Complaints," Comment No. C0008, Docket No. 78N-0301, Dockets Management Branch.

(4) Roth, S. H., "Myoflex Arthritis Study," Comment No. C0008, Docket No. 78N-0301, Dockets Management Branch.

(5) Batterman, R. C., and J. F. Sanders, "Myoflex Creme in Patients with Arthritic Involvement of the Hand," Comment No. C00008, Docket No. 78N-0301, Dockets Management Branch.

(6) Golden, E. L., "A Double-Blind Comparison of Orally Ingested Aspirin and a Topically Applied Salicylate Cream in the Relief of Rheumatic Pain," *Current Therapeutic Research*, 24:524-529, 1978.

(7) Altschuler, S., and E. Golden, "Double-Blind Comparison of Triethanolamine Salicylate with a Placebo for Pain Relief from Muscular Skeletal Pain," Comment No. C00007, Docket No. 78N-0301, Dockets Management Branch.

(8) Patel, A., and P. A. Chappelle, "Summary of TEA Clinical Trials in France, 1976-77," Comment No. C0007, Docket No. 78N-0301, Dockets Management Branch.

(9) Letter from W. E. Gilbertson, FDA, to W. L. Myers, Warren-Teed Laboratories, June 19, 1981, coded LET003, Docket No. 78N-0301, Dockets Management Branch.

(10) Letter from W. E. Gilbertson, FDA, to E. L. Steinberg, Thompson Medical Co., June 19, 1981, coded LET 004, Docket No. 78N-0201, Dockets Management Branch.

(11) Comment Nos. CP, SUP002, CR001, AMD, and AMD002, Docket No. 78N-0301, Dockets Management Branch.

Comments on Combination Products

8. One comment argued against the Category III classification of a combination product containing two Category I ingredients and one ingredient classified in Category III for effectiveness. The comment objected to the entire product being placed in Category III, according to the Panel's recommendations, when there has been no question of the product's safety or the effectiveness of the two Category I active ingredients. The comment argued that rather than require reformulation of the product, which would require research, stability testing, and quality

control testing, relabeling to indicate that the Category III ingredient is an inactive ingredient should be permitted.

The agency has published a proposed rule dealing specifically with the use of inactive ingredients in OTC drug products. (See the Federal Register of April 12, 1977 (42 FR 19156).) The proposal identified suitable physical or technical functions (e.g., denaturing agents, emollients, dispersing agents) that an inactive ingredient must perform to be regarded as appropriate for use in OTC drug products. The rule proposed to preclude the retention and redesignation of an active ingredient as an inactive ingredient unless it performs one of these functions. Although this proposal has not yet been published as a final rule, the agency does not sanction arbitrary redesignation to inactive status of ingredients that were submitted as active ingredients and for which data are insufficient to show effectiveness. If such ingredients were retained in a formulation and designated inactive, consumers would be needlessly exposed to them without any corresponding benefit. Many ingredients that are generally recognized as safe are still capable of causing side effects, allergic reactions, etc.

Paragraph 5 of the agency's "General Guidelines for OTC Drug Combination Products" (Ref. 1) provides that "In some cases an ingredient may be appropriate for use only in a specific combination or data may be available only to support the use of the ingredient in combination but not as a single ingredient. In such cases the ingredient will be placed in Category I for use only in permissible combinations and not as a single ingredient." The comment did not mention the specific ingredients contained in its product, nor did it submit any data to support the use of the Category III ingredient in the combination product only. If data are submitted to support the use of the ingredient in the combination, i.e., showing contribution to the claimed effect, as required by 21 CFR 330.10(a)(iv), then it could be classified as Category I for use in the specific combination but not as a single ingredient.

Reference

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

9. One comment, from the author of the Panel's minority report on combination products (44 FR 69787-69790), suggested a number of changes in the minority report, which, the comment stated, would make it consistent with the agency's general guidelines for OTC drug combination products (Ref. 1), which were published after the Panel had adopted its report. The comment requested that this minority report, with suggested revisions, replace the combination policy recommended by the majority of the Panel members in § 348.20, adding that such a replacement would eliminate the provisions of the majority report that have no therapeutic or scientific basis.

The agency accepts the changes in the minority report and has considered these revisions along with the combination policy developed by the majority of the Panel and other comments received (see comment 8 above and comments 10, 11, and 12 below). The agency's proposed regulations for combinations of OTC external analgesic active ingredients, based on the consideration of all these factors, are set forth in § 348.20 of this tentative final monograph. The agency believes these proposed regulations have therapeutic and scientific bases and are consistent with the regulations governing combinations of OTC active ingredients in § 330.10(a)(4)(iv) and the agency's supplementary quidelines (Ref. 1). Therefore, the agency sees no reason for the revised minority report to replace the combination policy recommended by the majority of the Panel.

Reference

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

10. One comment supported the combination policy recommended by the majority of the Panel (44 FR 69785), but objected to limiting combination products to no more than one active ingredient from each specified group in § 348.20 (a), (b), and (c). The comment requested that more than one ingredient from each group be permitted provided that the combination conforms with the OTC drug review regulations (§330.10(a)(4)(iv)).

The combination policy in § 330.10(a)(4)(iv), as supplemented by the agency's general guidelines for OTC drug combination products (Ref. 1), specifies the criteria for OTC combination drug products. The agency's guidelines state that ingredients from the same therapeutic category that have different mechanisms of action may be combined to treat the same symptoms or condition if the combination meets the OTC combination policy in 21 CFR 330.10(a)(4)(iv) in all respects and the combination is, on a benefit-to-risk basis, equal to or better than each of the active ingredients used alone at its therapeutic dose. The guidelines also state that Category I active ingredients from the same therapeutic category that have the same mechanism of action should not ordinarily be combined unless there is some advantage over the single ingredient in terms of enhancing effectiveness, safety, patient acceptance, or quality of formulation. Thus, the combination policy in § 330.10(a)(4)(iv) and the agency's supplementary guidelines do not limit the number of ingredients from the same pharmacologic group that may be combined, provided data are presented to show that the combination meets the necessary criteria. The comment, however, did not submit any such data. Combinations containing ingredients from the same pharmacologic group will be permitted if adequate data are presented to the agency, and § 348.20 will be amended accordingly.

Reference

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

11. One comment requested that hydrocortisone be allowed in combination with the ingredients in group II A (the "caine" type analgesics) listed at 44 FR 69786. The comment argued that to prohibit such combinations is a departure from the combination policy set forth in 21 CFR 330.10(a)(4)(iv), that the marketing history of these combinations in prescription products dose not show any adverse reactions, and that the effectiveness of such combinations is well documented by the effectiveness of the individual ingredients. Another comment requested that hydrocortisone combinations not be classified in Category II because there are various other pharmacological categories of drugs that can properly be combined with hydrocortisone, such as antifungal agents or skin protectants. The comment requested that consideration be given to including under § 348.20(b) combinations of hydrocortisone with the other ingredients listed under recommended § 348.10(b).

The agency does not agree with the comments that hydrocortisone should be allowed to be marketed OTC in combination with other external analgesic active ingredients at this time. The "caine"-type analgesics have indications similar to hydrocortisone, but have different mechanisms of

FDA's General Guidelines for OTC Drug Combination Products allow for such combinations if the combination is on a benefit-to-risk basis equal to or better that each active ingredient used alone at its therapeutic dose (Ref. 1). However, no evidence has been submitted demonstrating that the combination of hydrocortisone with a "caine" analgesic would meet this criterion. If such data are received, the agency will consider an addition to § 348.20.

The agency notes that the Panel's recommended monograph for skin protectant drug products, published in the **Federal Register** of August 4, 1978 (43 FR 34628), provides for certain skin protectants to be labeled for the symptoms of oozing or weeping due to poison oak or poison ivy (§ 347.50(b)(6)), while the recommended monograph for external analgesic drug products includes relief of minor skin irritations, itching, and rashes due to poison oak or poison ivy in the label indication for hydrocortisone (§ 348.50(b)(3)). The agency therefore will consider the combination of a skin protectant with hydrocortisone for treatment of the symptoms of poison oak or poison ivy if data to support such a combination are submitted. Combinations of antifungal agents and hydrocortisone were considered by the Antimicrobial II Panel in its report on antifungal drug products, published in the **Federal Register** of March 23, 1982 (47 FR 12480). Such combinations will be addressed in that rulemaking.

Reference

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

12. One comment stated that the Panel's recommendations is § 348.20(a) would not allow a combination of camphor and menthol, but would allow a combination of camphor, menthol, and certain other external analgesic active ingredients. The comment requested that § 348.20(a) be amended to allow combination products containing only camphor and menthol as the active ingredients.

The agency agrees with the comment that the monograph should provide for combination products containing camphor and menthol as the only active ingredients. The omission of this combination appears to have been an oversight. Accordingly, the agency is proposing to amend § 348.20 by adding new paragraph (a)(6) to read as follows:

(6) Camphor identified in § 348.12(b)(1) may be combined with menthol identified in § 348.12(b)(2).

13. One comment stated that the Panel's recommended concentration limits for phenol and camphor are not appropriate for a product containing a complex of the two ingredients and requested that 4.7 percent phenol combined with 10.8 percent camphor in light mineral oil be permitted in analgesic, anesthetic, and antipruritic drug products. The comment argued that the clathrate complex that is formed when camphor is combined with phenol significantly reduces the available phenol and camphor. The comment submitted data to show that the combination is less irritating than the same amout of phenol or camphor alone and added that, based on actual consumer use, a product containing this camphor/phenol combination produces remarkably little irritation or erythema (Ref. 1).

Another comment from a manufacturer of products containing comphorated metacresol, which is composed of camphor and metacresol in a 3-to-1 ratio, objected to the Category III status of 1 to 3 percent camphorated metacresol and the Category II status of camphorated metacresol over 3 percent concentration (Ref. 2). The comment explained that the action of cresol is not associated with protein binding and would not therefore encourage continued release of "free" metacresol. The comment stated that toxic doses of cresol far exceed the quantities released even by products containing 88 percent camphorated metacresol. The comment argued that its products, which contain from 4 to 88 percent camphorated metacresol (composed of 1 to 22 percent metacresol and 3 to 66 percent camphor), should be placed in Category I based on their long history of safe use, and on data showing that metacresol is the least toxic of the cresols, that metacresol is less toxic than phenol, and that the rate of absorption of metacresol depends more on the area covered than on the concentration (Ref. 3).

The Agency agrees with the comment and the Panel that phenol combined with camphor can be safely used at a higher concentration than phenol used alone. Since the Panel adopted its report, the agency has verified that the amount of free phenol is reduced when camphor and phenol are combined (Ref. 4). Although the Panel recommended in its monograph a maximum level of 2 percent phenol and did not provide for a different concentration of phenol in combination with camphor, the Panel stated in its report that "When camphor is added to phenol, a liquid forms. This reduces the severity of the topical reaction and the absorption of phenol * * *" (44 FR 69833). In addition, the summary minutes of the Panel's seventh meeting indicate that the Panel intended to place the combination of 4.7 percent phenol and 10.8 percent camphor into Category I for both safety and effectiveness (Ref. 5). The Panel concluded that both phenol and camphor as single ingredients are Category I. The Panel's Category I recommendation for the complex was inadvertently omitted from its recommended monograph.

Another panel, the Advisory Review Panel on OTC Antimicrobial Drug Products (Antimicrobial I Panel), stated that "when camphor is used with phenol in an oil formulation, the concentration of phenol should be no more than 5 percent" (39 FR 33133). In reviewing data on camphor/phenol combinations, the Antimicrobial I Panel concluded that "the presence of camphor also retards the absorption of phenol after topical application. A 1-hour exposure of the rat tail to a 4.8 percent aqueous phenol solution resulted in the absorption of 71 mg of phenol; whereas, the exposure to 10.9 percent camphor combined with 4.5 percent phenol resulted in the absorption of only 16 mg phenol" (39 FR 33122). The agency concluded in the tentative final monograph for OTC topical antimicrobial drug products "that the total concentration of phenol in powders and in aqueous, alcoholic or oil formulations be restricted to less than 1.5 percent. When camphor is used with phenol in an oil formulation, the concentration of phenol should be no more than 5 percent" (43 FR 1238). To reduce the irritating potential of phenol when concentrations of 4.7 percent are used, camphor must be present in excess of that concentration (Refs. 1 and 4). Accordingly, the agency is proposing that 4.7 percent phenol, when it is combined with 10.8 percent camphor, be included in the tentative final monograph. The agency is proposing to add new paragraph (b)(4) to § 348.20 to read as follows:

(4) Camphor and phenol identified in § 348.10(b)(3) and (8) may be combined in a light mineral oil, USP vehicle.

At this time, the agency is proposing to restrict the vehicle to light mineral oil, USP, because safety and effectiveness have been established in that vehicle only. Different vehicles can change the irritating properties of the combination (Refs. 6 and 7). There is evidence that vehicles containing glycerin or gelling agents such as silicon dioxide can increase the irritating properties of the combination (Ref. 7). Therefore, all other vehicles are classified as Category III at this time. Interested persons may submit data to support the use of other vehicles.

Regarding camphorated metacresol, the Panel stated that it is either a "complex" formed by the interaction of camphor with metacresol or a solution of the cresol in camphor. Since the panel adopted its report, the agency has determined that metacresol behaves similarly to phenol with respect to bonding with camphor and therefore can be considered a "complex" and categorized as camphorated metacresol (Ref. 4).

As a single ingredient, metacresol was not reviewed by the Panel. However, it has been shown to be somewhat less toxic than phenol based on the following LD_{50} data (Ref. 3):

LD_{50} METACRESOL AND PHENOL (IN G/KG)

Species	Route	Meta-cresol	Phenol
Rabbit	Subcutaneous	0.50	0.50
Cat	Subcutaneous	0.18	0.08
Mouse	Subcutaneous	0.45	0.35
Cat	Intravenous	0.28	0.18

The results indicate that the range of acute toxicity of metacresol is similar to phenol.

Based on the available information, which includes recognition of the combination of phenol and camphor as Category I, data showing metacresol is equal to or less toxic than phenol, and the new data showing that metacresol bonds to camphor similarly to phenol, the agency concludes that camphorated metacresol is Category I but only when prepared from camphor and metacresol combined in a 3-to-1 ratio not to exceed a concentration of 10.8 percent camphor. Based on a 3-to-1 ratio of camphor to metacresol with a limit of 10.8 percent camphor, the upper limit for metacresol is 3.6 percent. This 3-to-1 ratio results in reduced irritation (Ref. 2). The agency is proposing a lower limit of 1 percent metacresol based on information on marketed products submitted by the comment (Ref. 2). Accordingly, the agency is proposing to add new paragraph (b) to § 348.3, *Definitions*, in this tentative final monograph to read as follows:

(b) *Camphorated metacresol.* a complex consisting of camphor and metacresol combined in a ratio of 3 parts camphor to 1 part metacresol.

The comment did not provide sufficient data to establish general recognition of safety of a concentration of metacresol greater than 3.6 percent when this ingredient is combined with camphor. The studies reviewed by the Panel and the studies submitted by the comment (Ref. 2) were very limited in scope and are inadequate to demonstrate safety of higher concentrations. Most of the animal toxicity studies tested only one animal, observed the animal only for a short period of time, and did not include a detailed examination of the animal following drug application. The comment's statements about rate of release of metacresol are unproven because the comment submitted no information on the quantity of metacresol released under the conditions of use. The comment also did not submit any data to support the safety of concentrations of camphor above 10.8 percent.

In regard to the comment's claim of "long history of safe use," marketing history alone cannot be regarded as adequate proof of safety. The safety of camphorated metacresol as an external analgesic above the established dosage (not to exceed 3.6 percent metacresol and 10.8 percent camphor) has not been established, and therefore concentrations above this dosage remain in Category III.

References

(1) Comment No. C0013, Docket No. 78N–0301, Dockets Management Branch.

(2) Comment No. C0006, Docket No. 78N–0301, Dockets Management Branch.

(3) Public Health Service, The National Institutes of Health, "Phenol and Its Derivatives: The Relation Between Their Chemical Constitution and Their Effect on the Organism," by W. F. Von Oettingen, National Institutes of Health Bulletin, No. 190, pp. 59–71, 1949.

(4) "OTC Drugs," (Camphor and Phenol). Semiannual Report of Laboratory Activities, Bureau of Drugs, Food and Drug Administration, October 1981 to July 1982, Docket No. 78N–0301, Docket Management Branch.

(5) Summary minutes of Seventh Meeting of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products, p. 4, January 30 and 31, 1974, included in OTC Volume 06BPA2.

(6) Deichmann, W. B., T. Miller, and J. B. Roberts, "Local and Systemic Effects Following Application of Dilute Solutions of Phenol in Water and in Camphor-Liquid Petrolatum on the Skin of Animals," *Archives of Industrial Hygiene and Occaptional Medicine*, 2:454–461, 1950.

(7) Sterling-Winthrop Research Institute, "Eye and Skin Irritation Study with Campho-Phenique Gel in the Rabbit," Table III, unpublished study, September 26, 1977, Comment No. C0013, Docket No. 78N–0301, Dockets Management Branch.

D. Comment on Testing of External Analgesic Drug Products

14. One comment suggested several methods for testing the actions, effects, and efficacy of external analgesic ingredients. These included a laboratory animal study utilizing trolamine salicylate tagged with Carbon-14 to determined the degree of local penetration and distribution of this ingredient and developing a model to study the effects of topically applied trolamine salicylate on local tissue prostaglandin levels. In addition, the comment suggested a method of testing external analgesic ingredients in humans that is detailed in a published study and involves inducing muscle soreness by a controlled amount of exercise and measuring the bioelectrical activity of the muscle by electromyography before and after external analgesic use to determine muscle soreness and the extent of drug activity (Ref. 1).

In the **Federal Register** of September 29, 1981, (49 FR 47740), the agency published a policy statement that included procedures for the submission and review of proposed testing protocols, for agency meetings with industry or other interested persons, and for agency communications on submitted test data and other information. Under this policy, the agency provides consultation on protocols or testing guidelines, but these communications are not included in the administrative record for the related OTC drug monograph unless they directly influence an agency decision on a particular matter in the monograph or provide the substantiation for the agency's decision on that matter. For example, a protocol or test guideline would not normally become part of the administrative record, but the results of the study would be included in the administrative record. The testing methods suggested by the comment do not influence the agency's decision on the Category III status of trolamine salicylate; therefore, they will not be discussed further in this document.

Reference

(1) White, J. R., and J. N. Sage, "Topical Analgesic on Induced Muscular Pain," *Physical Therapy*, 50:166–172, 1970.

E. Comments on Labeling of External Analgesic Drug Products

15. Several comments objected to the agency's policy of specifying a limited list of terms as the only permissible indications for external analgesic products. One of the comments argued that it is improper and inappropriate to legislate the use of words and phrases through a rulemaking. One comment stated that the agency lacks statutory authority to prescribe exclusive lists of terms. All the comments requested that the final monograph allow the use of alternative or additional labeling terms that are truthful, accurate, not

misleading, and intelligible to the consumer.

During the course of the OTC drug review, the agency has maintained that a monograph describing the conditions under which an OTC drug will be generally recognized as safe and effective and not misbranded must include both specific active ingredients and specific labeling. (This policy has become known as the "exclusivity rule.") The agency's position has been that it is necessary to limit the acceptable labeling language to that developed and approved through the OTC drug review process in order to ensure the proper and safe use of OTC drugs. The agency has never contended, however, that any list of terms developed during the course of the review literally exhausts all the possibilities of terms that appropriately can be used in OTC drug labeling. Suggestions for additional terms or for other labeling changes may be submitted as comments to proposed or tentative final monographs within the specified time periods or through petitions to amend monographs under § 330.10(a)(12). For example, the labeling proposed in this tentative final monograph has been expanded and revised in response to comments received.

During the course of the review, FDA's position on the "exclusivity rule" has been questioned many times in comments and objections filed in response to particular proceedings and in correspondence with the agency. The agency has also been asked by The Proprietary Association to reconsider its position. To assist the agency in resolving this issue, FDA conducted an open public forum on September 29, 1982 at which interested parties presented their views. The forum was a legislative type administrative hearing under 21 CFR Part 15 that was held in response to a request for a hearing on the tentative final monograph for nighttime sleep-aids and stimulants (published in the **Federal Register** of June 13, 1978; 43 FR 25544). The agency's final decision on this issue will be announced in the **Federal Register** following conclusion of its review of the material presented at the hearing.

16. One comment disagreed with the Panel's recommendations that inactive ingredients and the quantity of the ingredient be listed in the labeling of OTC external analgesic drug products. The comment argued that a list of inactive ingredients would be meaningless to all but a few consumers and that such a list might overemphasize the importance of the inactive ingredients, obscure more meaningful information such as warnings or directions for use, and be more confusing than helpful. The comment also stated that if the quantity of the inactive ingredients had to be listed there would be an additional problem of changing the labels whenever the quantity of an inactive ingredient is changed.

The agency agrees with part of the Panel's recommendation. The Federal Food, Drug, and Cosmetic Act does not require the identification of all inactive ingredients in the labeling of OTC drug products. Section 502(e) (21 U.S.C. 352(e)) does require disclosure of active ingredients and of certain ingredients, whether included as active or inactive components in a product. Although the inclusion of all inactive ingredients in OTC drug product labeling is not required, the agency urges manufacturers to list all inactive ingredients voluntarily, as suggested by the Panel. Consumers with known allergies or intolerance to certain ingredients could then select products with increased confidence of safe use.

With regard to listing the quantity of inactive ingredients, section 502(e) (21 U.S.C. 352(e)) limits the requirement for stating the quantity of active ingredients in OTC labeling to those specifically named in that section. The agency cannot require listing of the quantity of any ingredient, whether active or inactive, in OTC drug products, except those designated in the act.

17. One comment questioned the Panel's qualifications and competence to evaluate and judge what message was being communicated to the consumer, expressed in lay terms, in its recommended labeling. The comment stated that in many cases the words and phrases recommended by the Panel were based on the Panel's own perceptions as to what the terms communicate to the consumer and that the Panel did not provide any documentation, surveys, etc., to support its findings.

Since its inception, the OTC drug review has focused on developing labeling of OTC drug products that can be understood by the average consumer. While the agency acknowleges that professional experience in mass communication was not a criterion for participation in the OTC drug advisory review panels, the clinical background of the physicians, pharmacists, and other health professionals on each panel involved direct experience with patients and an awareness of the terms used by them to refer to their symptoms. In addition to members of the scientific and medical communities, each panel included representatives from industry and consumer groups and thus had access to the experience of these groups in mass communication of medical terminology. Finally, any citizen interested in doing so could participate in the OTC drug review by presenting views at panel meetings, and, now that the panels have concluded their reviews, by commenting on advance notices of proposed rulemaking or by commenting or objecting to tentative final monographs proposed by the agency. A number of changes in the Panel's recommended labeling of external analgesic products have been incorporated into the agency's proposed labeling as a result of comments received. The agency urges anyone having suggestions for making the labeling language used in the external analgesic final monograph more understandable to the average consumer to submit these suggestions in comments responding to this document. After a final monograph for external analgesic drug products is issued, such suggestions may be made in the form of a petition to amend the monograph according to the procedures described in 21 CFR 10.30.

18. One comment to the advance notice of proposed rulemaking for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products (published in the **Federal Register** of September 9, 1976; 41 FR 38312) requested that OTC external analgesic drug products be included in the table at 41 FR 38320 that listed specific symptoms and the corresponding pharmacologic groups of drugs for the treatment of these symptoms. The comment suggested that item 8 of the table, "Generalized aching," be expanded to include the Category I labeling indications for topical analgesics, counterirritants, and rubefacients recommended by the Topical Analgesic Panel.

The agency does not agree that external analgesic drug products are suitable for inclusion in item 8 of the Cough/Cold Panel's table because this inclusion would imply that external analgesics should be labeled for relief of symptoms of aching due to common cold. The agency is not aware of any data, nor were any submitted, indicating that these products are effective in relieving symptoms of aching due to the common cold. If such data are submitted in the future, the agency will reconsider this claim.

19. One comment suggested that the claims not reviewed by the Topical Analgesic Panel but considered by other panels (e.g., "antiseptic," "fungistatic for

athlete's foot") and claims deferred to other panels (e.g., "pain due to hemorrhoids," "piles.") should not have been listed under Category II labeling in paragraphs (d) and (e) (44 FR 69845), but should have been left unclassified, pending classification by the appropriate panels.

The agency agrees with the comment that the claims under (d) and (e) at 44 FR 69845 should not be classified in Category II in the rulemaking for external analgesic drug products. These claims have been deferred to other panels and are covered in separate rulemaking proceedings. With the exception of claims relating to diaper rash, these claims will no longer be considered in this rulemaking. Drug products for the treatment of diaper rash were reviewed by the Advisory Review Panel on OTC Miscellaneous External Drug Products, which recommended that some of the ingredients in those drug products be evaluated in the external analgesic rulemaking. As noted above the **Federal Register** of September 7, 1982 (47 FR 39412) included a notice of reopening of the administrative record to include the Miscellaneous External Panel's statement on drug products for the treatment of diaper rash. The agency will address the use of external analgesic active ingredients for the treatment of diaper rash in this rulemaking in a future **Federal Register** publication.

20. One comment stated that there is no evidence that the term "external analgesic," the Panel's recommended statement of identity, is more informative to consumers than other terms such as "topical analgesic" or "pain relieving ointment." The comment suggested that the latter terms be allowed in addition to "external analgesic."

The agency agrees that the terms referred to by the comment would be as informative to consumers as the Panel's recommended statement of identity. Therefore, the agency is proposing the following alternative statements of identity in § 348.50(a)(1): "The labeling identifies the product as an 'external analgesic,' 'topical analgesic,' or 'pain relieving (*insert dosage form, e.g., cream, lotion, or ointment*).' "

21. Several comments requested that the statement of identity for OTC hydrocortisone products be changed from "antipruritic" to "anti-itch." The comments argued that "antipruritic" is a technical term that would not be understood by most consumers and that the term "anti-itch" would be more meaningful.

The agency agrees with the comments that the term "antipruritic" may not be well understood by many consumers and, if used, should be associated with a nontechnical term. Accordingly, the following statements of identity are being proposed for hydrocortisone products in § 348.50(a)(2): "antipruritic (anti-itch)," "anti-itch," and "antipruritic (anti-itch)" or "anti-itch" followed by a description of the dosage form, e.g., "anti-itch cream."

22. One comment stated that hydrocortisone is probably not effective for the relief of itching due to insect bites, or for contact dermatitis due to poison ivy, oak, and sumac and that more potent corticosteroids are usually required for these problems. Another comment questioned "whether consumers can accurately diagnose contact 'dermatitis' due to 'poison oak' or 'poison sumac'" and added that the labeling terminology should be revised.

The agency is aware that severe skin inflammation caused by poison ivy does not respond to topically applied hydrocortisone, and that even the stronger halogenated steroids are not effective when used topically in such instances. Severe poison ivy often requires systemic steroid therapy. Topically applied hydrocortisone is also not effective in relieving severe reactions to insect bites. However, the itching due to mild poison ivy and to normal reactions to insect bites is relieved by topical hydrocortisone at OTC strength (Refs. 1, 2, and 3). The agency believes that the words "temporary" and "minor" in the indications for hydrocortisone are sufficient to alert consumers to the appropriate use of this ingredient. The agency is proposing deletion of the word "dermatitis" from the OTC hydrocortisone label because this word is not apt to be readily understood by consumers. This word is suitable for professional labeling, and a closely related term, "dermatoses," is included under "Indications and Usage" in the agency's class labeling guideline for topical corticosteroids (Ref. 4). Manufacturers should follow this guideline in developing professional labeling for hydrocortisone drug products. The terms "poison oak" and "poison sumac" are retained in the proposed OTC labeling because these plants and the rash and itching they cause are familiar to consumers who live in areas in which the plants are found.

References

(1) Letter from A. M. Kligman to C. C. Evans, FDA, November 3, 1980, Docket No. 78N–0301, Dockets Management Branch.

(2) Fisher, A. A., "Contact Dermatitis," 2d Ed., Lea and Febiger, Philadelphia, pp. 264–265, 1973.

(3) Domonkos, A. N., H. L. Arnold, and R. E. Odom, "Andrews' Diseases of the Skin," 7th Ed., W. B. Saunders Co., Philadelphia, p. 559, 1982.

(4) Food and Drug Administration, "Topical Corticosteroids Class Labeling Guideline," Docket No. 81D–0274, Dockets Management Branch.

23. One comment stated that, because the claim "relief of cuts, scratches, abrasions, wounds, etc.," is similar to indications recommended by the Panel in § 348.50(b)(2), the Panel must have inadvertently included this claim under Category II labeling at 44 FR 69844–69845.

The Panel concluded that the above claim was confusing and meaningless to consumers because external analgesic drug products relieve the pain of cuts, scratches, abrasions, wounds, etc., but do not provide "relief of cuts * * * ". The agency concurs with the Panel's Category II classification of this claim.

24. One comment argued that there is a need for a distinction between the labeling of topical analgesic and topical anesthetic ingredients. The comment stated that the Panel had differentiated between analgesics and anesthetics through distinct definitions in § 348.3(d) and (e), by establishing separate subgroups of external analgesics (44 FR 69786), and in its combination policy. The comment pointed out that topical analgesics depress cutaneous sensory receptors without necessarily abolishing other sensations (i.e., cause a partial blocking of subcutaneous terminal nerve endings), whereas topical anesthetics completely block pain receptors, resulting in a sensation of numbness. The comment concluded that consumers should be informed of these distinctions and suggested the following examples of wording that could be used in the indications for topical anesthetic ingredients: "complete temporary relief * * *," "completely blocks * * *," "temporarily stops * * *," "completely stops * * *."

The agency does not agree that there is a need for a distinction between the labeling of topical analgesic and topical anesthetic products. In use, the effect of topical anesthetics is indistinguishable from the effect of topical analgesics. Topical anesthetics are theoretically capable of completely blocking pain receptors, but factors may affect the penetration of topical anesthetics through the skin and prevent complete blocking of the subcutaneous pain receptor site. Some of the factors affecting penetration of topical

anesthetics through the skin are as follows: (1) Drugs more readily penetrate to the subcutaneous receptor sites through damaged skin than through intact skin. Therefore, the effect of topical anesthetic products may be enhanced when they are applied to abraded, scratched, or burned skin. (2) Drugs penetrate hydrated skin and thin skin (for example, in the groin area) more readily than thick skin (such as on the palms of the hands). (3) Penetration may be affected by certain disease conditions such as eczema, which causes thinning of the skin; by product formulation; or by ionization of the active ingredient.

Because of these factors and because the Panel felt that there is no recognizable difference in effectiveness between anesthetics and analgesics, the Panel recommended that topical analgesics and anesthetics that depress cutaneous sensory receptors bear the same indication: "For the temporary relief of minor aches and pains of * * *". The agency believes that consumers would be misled if an external analgesic product were labeled as providing "complete temporary relief," "completely stops," or "completely blocks" minor aches and pains. The agency concurs with the Panel's recommended wording ("for the temporary relief of") and is proposing this wording in the tentative final monograph.

25. Two comments stated that the following language should be allowed in the labeling of external analgesic drug products, based on language that was not recommended by the Panel but was contained in its report: "for relief of pain in joints, muscles, tendons," "relieves pain without causing numbness," "completely blocks pain receptors," "relieves pain by reducing inflammation," "numbs and abolishes responses to painful stimuli," and "rheumatism."

The Panel allowed the claim "for the temporary relief of minor aches and pains of muscles and joints." The agency concurs with the Panel that the indications for OTC external analgesic drug products should emphasize that these products relieve only minor pain and have an action that is only temporary. The Panel did not review data on the use of external analgesic drug products for relief of pain in tendons, nor did the comment submit any data. Thus the agency is not proposing a claim for relief of pain in tendons until data are submitted to demonstrate the effectiveness of external analgesic drug products at these sites.

Claims regarding numbness or similar claims, such as completely blocking pain receptors or abolishing responses to painful stimuli, may be misleading to consumers because the manner in which external analgesic drug products are used determines whether they cause numbness or not. For example, the application of a product on abraded skin may cause numbness because of increased absorption that occurs, whereas application of the same product on intact skin may not cause numbness. (See comment 24 above.)

The agency believes that the term "reducing inflammation" should not be included as an indication—except when the term "inflammation" is used as a descriptive term related to the relief of itching associated with the nonserious conditions in the recommended indication for hydrocortisone and hydrocortisone acetate. (See comment 29 below for further discussion.) While the terms "arthritis" and "rheumatism" are used interchangeably by some consumers, "arthritis," the more accurate and precise term, is more readily understood by the majority of consumers. Substituting the term "rheumatism" probably would not increase consumers' understanding of the use of counterirritants and might cause confusion. In addition, the agency proposes to delete the terms "lumbago" and "neuralgia" from the Panel's recommended labeling in § 348.50(b)(1) because they are not readily understood by consumers. The revised indication in § 348.50(b)(1) for external analgesic products containing counterirritant active ingredients is as follows: "For the temporary relief of minor aches and pains of muscles and joints" [which may be followed by: "associated with" (select one or more of the following: "simple backache," "arthritis," "strains," "bruises," and "sprains.")]

26. Three comments disagreed with the Panel's placement of claims such as "relief of deep-seated pain," "deep strength," and "penetrating heat relief" in Category III. The comments claimed this classification was inconsistent with various statements made by the Panel about the mechanism of action of counterirritants (44 FR 69779), and the following statement regarding methyl salicylate: "methyl salicylate acts as a counterirritant for the temporary relief of deep-seated pain" (44 FR 69830). The comments maintained that relief of "deep-seated pain" is an established benefit of counterirritant ingredients, and that claims such as "deep strength," "penetrating heat relief," and "relief of deep-seated pain" should be acceptable claims along with claims such as "penetrating relief" that were found acceptable by the Panel.

One comment argued that the following labeling terms that the Panel placed in Category II are not misleading or meaningless to consumers: "fast," "swift," "sudden," "immediate," "prompt," "poignant," and "bright." The comment added that the Panel did not give any reason why the term "fast" was considered misleading. Another comment stated that studies submitted to the Panel show that certain external analgesic ingredients do act within minutes, and their action may be considered "fast" in layman's terms, pointing out that the Panel failed to describe what time period would be acceptable as "fast," i.e., what data it considered sufficient to support this claim.

The OTC drug review program establishes conditions under which OTC drugs are generally recognized as safe and effective and not misbranded. Two principal conditions examined during the review are allowable ingredients and allowable labeling. The FDA has determined that it is not practical—in terms of time, resources, and other considerations—to set standards for all labeling found in OTC drug products. Accordingly, OTC drug monographs regulate only labeling related in a significant way to the safe and effective use of covered products by lay persons. OTC drug monographs establish allowable labeling for the following items: product statement of identity; names of active ingredients; indications for use; directions for use; warnings against unsafe use, side effects, and adverse reactions; and claims concerning mechanism of drug action.

As with all OTC drug products, external analgesics are expected to achieve their intended results within a reasonable preiod of time. However, the specific period of time within which external analgesics achieve these results is not related in a significant way to the safe and effective use of the products. Therefore, terms such as "fast," "prompt," "swift," "sudden," and "immediate" would not signal any property that is important to the safe and effective use of these products, and these terms are outside the scope of the OTC drug review. For other classes of products in the OTC drug review, however, statements relating to time of action may properly fall within the list of terms covered by the mongraph. Likewise, claims concerning nontherapeutic characteristics of drugs such as color, odor, or touch (e.g., "bright," "poignant," "pleasantly scented," or "greaseless"), as discussed

by the Panel at 44 FR 69784–69785, are not dealt with in OTC drug monographs. The agency emphasizes that even though these terms are outside the scope of the OTC drug review, they are subject to the prohibitions in section 502 of the act (21 U.S.C. 352) relating to labeling that is false or misleading. Such terms will be evaluated by the agency in conjunction with normal enforement activities relating to that section of the act. Moreover, any term that is outside the scope of the review, even though it is truthful and not misleading, may not appear in any portion of the labeling required by the monograph and may not detract from such required information.

Claims concerning characteristics of therapeutic performance (e.g., "penetrating heat relief") will be dealt with only in cases where they imply the existence of a characteristic that would be therapeutically significant for the drug in question, if proved. The agency tentatively concludes that the statement "penetrating heat relief" does not describe therapeutically significant performance characteristics and will not be dealt with in this monograph. Accordingly, "penetrating heat relief" has been deleted from the section on Category III labeling (444 FR 69857). For the same reason, statements such as "penetrating relief," "warm comforting relief," and "penetrating cooling action," which were found reasonable and informative to consumers by the Panel (44 FR 69785), will not be dealt with in this tentative final monograph. The claim "penetrating pain relief," however, does describe a therapeutically significant performance characteristic by explaining the effect of counterirritants in language easily understood by consumers. However, the agency agrees with the Panel that this statement and similar ones should not be included as indications (44 FR 69785). Accordingly, the agency is proposing new § 348.50(b)(4) in this tentative final monograph under the heading "Other allowable statements," to include statements describing pain relief, as follows:

(4) *Other allowable statements.* In addition to the required information specified in this paragraph and in paragraphs (a), (b), (c), and (d) of this section, the labeling of the product may contain any of the following statements, provided such statements are neither placed in direct conjunction with information required to appear in the labeling nor occupy labeling space with greater prominence or conspicuousness than the required information.

(i) For products containing any ingredient identified in § 348.12.

(*a*) (optional: "provides") "penetrating pain relief."

(*b*) (optional: "provides") "warming pain relief."

(*c*) (optional: "provides") "cool pain relief."

(ii) [Reserved]

The agency finds that the term "deep strength" is vague and conveys no useful information to consumers. A number of interpretations are possible. The term could refer to the extent of pentration of the drug, the potency or concentration of the drug, or the depth of action of the drug. The "depth" of action is dependent upon the absorption of the drug and not necessarily upon its concentration. Other interpretations are entirely possible. Because this term could be interpreted in various ways, the agency considers the term "deep strength" too confusing and vague and therefore does not propose to include it in this monograph. In addition, the agency has reviewed the references cited by the Panel at 44 FR 69830 (Refs. 1 through 5) in support of its statement that "methyl salicylate acts as a counterirritant for the temporary relief of deep-seated pain" and determined that these references do contain adequate data to establish that counterirritant active ingredients relieve pain distal to the site of application. Despite the Panel's statement, the agency concludes that claims for "relief of deep-seated pain" are not suitable for OTC counterirritants. Deep-seated pain may be caused by a serious condition not amenable to self-diagnosis and treatment. The claim is therefore not included in this monograph.

References

(1) Krantz, J. C., Jr., and C. J. Carr, "Pharmacological Principles of Medical Practice," 6th Ed., The Williams and Wilkins Co., Baltimore, p. 200, 1965.

(2) Swinyard, E. A., "Demulcents, Emollients, Protectives and Adsorbents, Antiperspirants and Deodorants, Absorbable Hemostatics, Astringents, Irritants, Sclerosing Agents, Caustics, Keratolytics, Antiseborrheics, Melanizing and Demelanizing Agents, Mucolytics, and Certain Enzymes," in "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by L. S. Goodman and A. Gilman, The Macmillan Co., New York, p. 993, 1970.

(3) Crossland, J., "Lewis's Pharmacology," 4th Ed., E. and S. Livingstone, London, pp. 562–563, 1970.

(4) Fulton, G. P., E. M. Farber, and A. P. Moreci, "The Mechanism of Action of Rubefacients," *The Journal of Investigative Dermatology*, 33:317–325, 1959.

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

27. One comment disagreed with the recommendation that hydrocortisone be used for itchy genital and anal areas. The comment was concerned about the potential for absorption of hydrocortisone when used in the anogenital area and contended that the Panel's recommended warning to discontinue use and consult a physician if symptoms persist for more than 7 days will be ignored by many patients, and that frequent and chronic use of hydrocortisone in the genital areas may cause problems such as progression of an infection, dermal atrophy, and striae.

The Panel reached its conclusion that topical hydrocortisone is safe for OTC use in concentrations up to 0.5 percent for itchy genital and anal areas after a careful study of its use on all areas of the body, at a wide range of concentrations, and for prolonged periods of time (44 FR 69817 to 69822). In addition, the Panel found that dermal atrophy and striae are generally associated with the more potent fluorinated corticosteroids and have been reported only rarely for hydrocortisone, and then only after long term or excessive use (44 FR 69817). Because these conditions can arise with long-term or excessive use, the agency is concerned about the adequacy of the Panel's recommended warning. Consumers may use hydrocortisone in the anogenital area for itching, which may be alleviated after a few days of treatment. If the hydrocortisone is then stopped, the itching may recur within a few days and the consumer may again use hydrocortisone. Consumers may go through several cycles of starting and stopping treatment with hydrocortisone and the Panel's 7-day warning would be inadequate to warn against such overuse. The agency believes that the warning should emphasize to consumer the need to consult a doctor not only fo conditions that do not respond to self-treatment, but also for those that recur after such treatment with hydrocortisone. For this reason, the agency is proposing to revise the Panel' recommended warning as follows: "If condition worsens, or if symptoms persist for more than 7 days or clear up and occur again within a few days, discontinue use of this product and consult a" (select one of the following: "physician" or "doctor").

The agency further believes that hydrocortisone products that bear the indication for external genital itching need to include a warning to inform women not to use the drug in the presence of vaginal discharge. A vagina discharge may be a symptom of an infection, for which hydrocortisone is not effective and professional treatmen is needed. Accordingly, the agency is

proposing the following warning in § 348.50(c)(7): "Do not use if you have a vaginal discharge. Consult a" (select one of the following: "physician" or "doctor").

The Panel recommended in § 348.50 (c)(1)(i) that all OTC external analgesic drug products bear the warning "for external use only." The agency believes it is necessary to emphasize that OTC drug products containing hydrocortisone are intended only for external use in the genital and anal areas and that this information should be included in the indications for use for these products. The agency is therefore proposing to change the wording of the indication for hydrocortisone to read: for relief of "* * * external (select one or more of the following: 'genial,' 'feminine,' and 'anal' itching." The term "feminine itching" has been added as an optional labeling term because it is a term that is commonly used and understood by consumers.

As will be discussed in the preamble of the advance notice of proposed rulemaking for OTC vaginal drug products, which will be published in a future issue of the **Federal Register**, three OTC advisory review panels have made recommendations to FDA pertaining to the use of various OTC drugs in and around the vagina.

The Antimicrobial II Panel recommended that certain antifungal drugs currently available only by prescription be considered generally recognized as safe and effective for "treatment of external feminine itching associated with vaginal yeast (candidal) infection." However, the agency dissented on the Panel's recommendation because of its concern about consumer's self-treating itching associated with a vaginal infection (47 FR 12480). While the agency disagrees with the use of OTC drug products to treat vaginal infections, the agency tentatively believes that hydrocortisone can be safely and effectively used OTC to relieve external itching around the vagina. The agency recognizes that consumers cannot identify the underlying causes of such itching, but is aware that hydrocortisone will produce symptomatic relief. If relief is not obtained or the itching recurs, the consumer is advised to discontinue use of the drug and to consult a doctor. The agency will further discuss the OTC use of antifungal drug products for this use in the tentative final monograph for that class of drugs.

In light of the different recommendations from the three panels, previous agency actions, and the comments submitted in response to the advance notice of proposed rulemaking for OTC antifungal drug products, there appears to be uncertainty regarding the use of OTC drug products for treating the system of external itching around the vagina. The agency is particularly concerned about (1) the ability of a woman to recognize the nature or cause of the itching in order to determine which kind of drug product to select to treat it, e.g., an antipruritic or antifungal for the external areas, including the vulva, and (2) whether one week of self-medicating with an OTC drug product containing hydrocortisone may pose an unacceptable delay in seeking professional attention if the symptom(s) are due to gonorrhea, trichomonas, candida, or other organisms which will not be eradicated by topical therapy with OTC drug products containing hydrocortisone. The agency is tentatively agreeing with the Topical Analgesic Panel that hydrocortisone can be safety used OTC for relief of itching if accompanied by appropriate warnings but is inviting specific comment on this issue, and particularly invites comment from gynecologists, family practitioners, and other health professionals.

28. One comment requested that the Panel's recommended indication for antipruritic ingredients in § 348.50(b) (2) be expanded to allow the general claim "for the relief of itching." The comment argued that there is no scientific basis for limiting the claim to itching due only to minor burns, sunburn, minor cuts, abrasions, insect bites, and minor skin irritations. The comment concluded that the antipruritic properties of the ingredients included in § 348.10(b) provide relief no matter what stimulates the local itching sensation, and consumers should be informed accordingly.

The agency agrees with the comment that products containing antipruritic ingredients should be allowed to use the indication "For the temporary relief itching" without listing examples of causes of itching. Such labeling would be clearly recognizable and meaningful to a consumer who was experiencing itching without knowing the cause. The agency is therefore proposing that products containing antipruritic ingredients may be labeled for itching only or for itching associated with one or more causes. The agency is also proposing the same type of alternative labeling for hydrocortisone products. In addition, in order to improve clarity and to simplify OTC labeling, the agency is proposing to use the word "scrapes" instead of "abrasions" in the proposed indication for antipruritics in § 348.50(b)(2).

Based upon the above discussion, and the discussion in comment 27 above, the following indications are being proposed in the tentative final monograph as § 348.50(b) (2) and (3):

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

(3) *For products containing any external analgesic active ingredients identified in § 348.10(d).* "For the temporary relief of itching associated with minor skin irritations and rashes" [which may be followed by: "due to" (select one or more of the following: "eczema," "insect bites," "poison ivy, poison oak, or poison sumac," "soaps," "detergents," "cosmetics," "jewelry,") and/or ("and for external" (select one or more of the following: "genital," "feminine," and "anal") "itching.")]

29. Several comments requested that the term "inflammation" be added to the indications for OTC hydrocortisone drug products or that the term "anti-inflammatory" be used as the statement of identity for these products. The comments stated that it is medically inaccurate and incomplete to categorize hydrocortisone only as an antipruritic or external analgesic, because the relief of itching or pain is secondary to its anti-inflammatory action. The comments pointed out that the principal pharmacologic action of hydrocortisone has long been recognized as anti-inflammatory, and consumers should be informed of this activity to allow proper use of the ingredient.

In its review of hydrocortisone, the Panel acknowledged that numerous studies over a 20-year period have demonstrated the effectiveness of topical hydrocortisone preparations as antipruritic (anti-itch) and anti-inflammatory agents and that hydrocortisone preparations are frequently used as anti-inflammatory agents (44 FR 69813–69824). Nevertheless, the Panel recommended that hydrocortisone for OTC use bear labeling related only to its anti-itch activity and recommended an indication statement that specified use for nonserious conditions that the Panel believed consumers could appropriately self-medicate with hydrocortisone.

The statement of identity is intended to communicate to consumers the principal intended action of a drug in terms that are meaningful to the layman. The agency agrees with the Panel that

the principal intended OTC use of hydrocortisone drug products is to relieve itching. As discussed in comment 21 above, the agency is proposing "anti-itch" as the statement of identity for OTC hydorcortisone drug products. Although hydrocortisone does have an anti-inflammatory action, as the comment and the Panel acknowledged, the agency does not believe that the term "anti-inflammatory" should be included in the OTC statement of identity for products containing hydrocortisone. Inclusion of the term "anti-inflammatory" in the statement of identity may suggest to consumers that the product is intended for self-medicating serious conditions that should be treated by a doctor. The term "anti-inflammatory" may be used in the professional labeling of products containing hydrocortisone, as described in the class labeling guideline for topical corticosteroids (Ref. 1).

As mentioned in comment 28 above, the agency believes that the Panel's recommended indication needs to be revised to emphasize the OTC use of hydrocortisone preparations to relieve itching. The agency further believes that "inflammation" could be included as an optional descriptive term in the indication statement for hydrocortisone, so long as it is related to the relief of itching associated with the nonserious conditions included in the recommended indication. Therefore, the agency is proposing the following optional indication to be added as § 348.50(b)(3)(ii) of the tentative final monograph: "For the temporary relief of itching associated with minor skin irritations, inflammation, and rashes due to" (select one or more of the following: "eczema," "insect bites," "poison ivy, poison oak, or poison sumac," "soaps," "detergents," "cosmetics," "jewelry,") (which may be followed by: "and for external" (select one or more of the following: "genital," "feminine," and "anal") "itching.") The agency believes that the above indication will inform consumers about the anti-inflammatory properties of hydrocortisone while limiting its OTC use to specific nonserious conditions and thus help to prevent misuse of hydorcortisone for inflammation associated with infection. Further, the agency believes that the warning proposed as § 348.50(c)(1)(iii), "If condition worsens, or if symptoms persist for more than 7 days or clear up and occur again within a few days, discontinue use of this product and consult a" (select one of the following: "physician" or "doctor,") provides additional protection to consumers against such misuse.

Reference

(1) Food and Drug Administration, "Topical Corticosteroids Class Labeling Guideline," Docket No. 81D-0274, Dockets Management Branch.

30. Two comments disagreed with the Panel's warning in § 348.50(c)(1)(iii), which states "If condition worsens, or if symptoms persist for more than 7 days, discontinue use of this product and consult a physician." The comments noted that existing FDA warnings for counterirritants and topical salicylates in 21 CFR 369.20 direct consumers to consult a physician if pain persists for more than 10 days. One comment stated that in light of the excellent safety record of external analgesic products and in the absence of any data to the contrary, the 10-day use limitation should be retained.

The agency agrees with the Panel that 7 days is sufficient time for the consumer to self-treat with external analgesic products before consulting a physician. If symptoms persist after 7 days, there may be an underlying disease or condition that requires a physician's diagnosis and treatment, and continuing to self-treat for more than 7 days may delay proper treatment. Furthermore, prolonged duration of use can increase the incidence of sensitivity and decrease effectiveness of external analgesic ingredients. As stated by the Panel at 44 FR 69781, these ingredients can have a direct irritating effect or may produce sensitization from prolonged or repeated contact with the skin. For example, the Panel pointed out that patients may develop tolerance to the effectiveness of tripelennamine hydrochloride and diphenhydramine hydrochloride or become sensitive to these drugs after more than 7 days of use (44 FR 69809 and 69839). When the final monograph for external analgesic drug products is published, those parts of § 369.20 covered by the monograph will be deleted.

31. One comment objected to the Panel's recommended warning in § 348.50(c)(2)(ii) for counterirritants, "Do not bandage." The comment argued that it is common practice in athletic training procedures to cover injuries after applying counterirritants either to protect clothing or to increase the stimulation of cutaneous receptors. The comment suggested that a warning such as "Bandage with caution" be substituted for the Panel's warning.

The agency agrees with the comment that it is desirable to protect clothing from stains by covering the application site, but believes that such covering should not be tightly applied. The agency is not aware of any evidence that the risk of adverse reactions to counterirritants increases when the application site is lightly covered, but is aware that under tight bandaging or occlusive dressing there is an increased risk of irritation, redness, or blistering. The Panel did not provide specific reasons for recommending the warning "Do not bandage" for counterirritants. However, counterirritants are, as the name itself implies, irritating, and occlusion by tight bandaging may increase their absorption through the skin. Therfore, it is proposed in this tentative final monograph that the Panel's recommended warning "Do not bandage" be revised to "Do not bandage tightly." The agency believes that this warning is more helpful to consumers because it provides more specific information and is therefore clearer than the warnings proposed by the comment.

32. One comment requested that the minimum age restriction for use of topical analgesic, anesthetic, and antipruritic ingredients be changed from 2 years to 6 months of age. The comment argued that because the Panel defined adult skin as "skin that is older than 6 months of age" (44 FR 69773), because the effect of occlusion under a diaper can be taken care of by use of an appropriate warning, and because a child under 2 years of age is well able to communicate pain by crying, these ingredients can be used safely on children over 6 months of age. In addition, the comment stated that these products are particularly useful for crawling infants who receive minor scratches, with related discomfort, that do not require a doctor's care.

The agency believes that external analgesic drug products should not be used on children under 2 years of age except as recommended by a physician. Although it is true that by 6 months of age a child's skin is similar to an adult with regard to drug absorption, there are enough other differences betwen adult and children under 2 years of age to require different standards of practice the use of drugs. Children 2 years of age above are just beginning to learn to communicate verbally in expressing their symptoms to a parent. At less than 2 years of age, the infant is more passive and less able to express and localize symptoms. Occlusion from a diaper, from lying on a waterproof mattress, or from body folds touching each other can enhance cutaneous absorption that can result in systemic effects in infants who do not have fully developed drug metabolism systems. Analgesic drugs can also be corrosive to infants' skin under occlusion. Parents could be warned against occlusion from a diaper

but it would be difficult to warn them adequately against less obvious occlusion. Therefore, the agency agrees with the Panel that limiting use of these products to children 2 years of age or older except under the advice and supervision of a physician is necessary to provide an adequate margin of safety.

II. The Agency's Tentative Adoption of the Panel's Report

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

1. *Summary of ingredient categories.* The agency has reviewed all the claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and concurs with the Panel's categorization of ingredients except for camphorated metacresol and methapyrilene hydrochloride. (See paragraphs 11 and 15 under "Summary of the Agency's Changes in the Panel's Recommendations" below.) For the convenience of the reader, the following tables are included as summaries of the categorization of active ingredients recommended by the Panel and proposed by the agency.

Analgesic, anesthetic, and antipruritic active ingredients	Panel	Agency
Aspirin	III	III
Benzocaine	I	I
Benzyl alcohol	I	I
Butamben picrate	I	I
Camphor	I	I
Camphorated metacresol	III	I
Chloral hydrate	II	II
Chlorobutanol	III	III
Cyclomethycaine sulfate	III	III
Dibucaine	I	I
Dibucaine hydrochloride	I	I
Dimethisoquin hydrochloride	I	I
Diphenhydramine hydrochloride	I	I
Dyclonine hydrochloride	I	I
Eugenol	III	III
Glycol salicylate	III	III
Hexylresorcinol	III	III
Hydrocortisone [1]	I	I
Hydrocortisone acetate [1]	I	I
Juniper tar	I	I
Lidocaine	I	I
Lidocaine hydrochloride	I	I
Menthol	I	I
Methapyrilene hydrochloride	I	II
Phenol	I	I
Phenolate sodium	I	I
Pramoxine hydrochloride	I	I
Resorcinol	I	I
Salicylamide	III	III
Tetracaine	I	I
Tetracaine hydrochloride	I	I
Thymol	III	III
Trolamine salicylate [2]	III	III
Tripelennamine hydrochloride	I	I

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

Counterirritant ingredients	Panel	Agency
Allyl isothiocyanate	I	I
Strong ammonia solution [1]	I	I
Camphor	I	I
Capsaicin	I	I
Capsicum	I	I
Capsicum oleoresin	I	I
Chloral hydrate	I	I
Eucalyptus oil	I	I
Histamine dihydrochloride	I	I
Menthol	I	I
Methyl nicotinate	I	I
Methyl salicylate	I	I
Turpentine oil	I	I

[1] Identified by the Panel as ammonia water, stronger.

2. *Testing of Category II and Category III conditions.* The Panel recommended testing guidelines for external analgesic drug products (44 FR 69857). The agency is offering these guidelines as the Panel's recommendations without adopting them or making any formal comment on them. (See comment 14 above.)

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 condition included in the review by following the procedures outlined in the agency's policy statement published in the **Federal Register** of September 29, 1981 (46 FR 47740). This policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Changes in the Panel's Recommendations

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the Panel's report and recommended monograph with the changes described in FDA's responses to the comments above and with other changes described in the summary below. A summary of the changes made in the Panel's conclusions and recommendations follows.

1. The agency is proposing to include the combination of camphor and menthol in this tentative final monograph in new § 348.20(a)(6). (See comment 12 above.)

2. The agency proposes that 4.7 percent phenol be included in this tentative final monograph when it is combined with 10.8 percent camphor in accordance with § 348.20(a)(4). (See comment 13 above.)

3. The agency proposes changing the term "antipruritic," the Panel's recommended statement of identity for hydrocortisone products, to "antipruritic (anti-itch)," "anti-itch," antipruritic (anti-itch) *(insert dosage form, e.g., cream, lotion, or ointment),"* or "anti-itch *(insert dosage form, e.g., cream, lotion, or ointment)."* (See comment 21 above.)

4. Alternatives to the Panel's recommended statement of identity, "external analgesic," are being proposed in § 348.50(a)(1) as "external analgesic," "topical analgesic," or "pain relieving *(insert dosage form, e.g., cream, lotion, or ointment)."* (See comment 20 above.)

5. The agency proposes that terms such as "fast," "prompt," "swift," "sudden," and "immediate," which were classified by the Panel as Category II, and statements such as "penetrating heat relief" are outside the scope of the OTC drug review because they do not signal any property that is important to the safe and effective use of OTC external analgesic drug products. Claims such as "penetrating pain relief" do describe therapeutically significant performance characteristics of OTC counterirritant active ingredients and are included under a new section, § 348.50(b)(4), "Other allowable statements." (See comment 26 above.)

6. The 7-day warning recommended by the Panel for external analgesic drug products in § 348.50(c)(1)(iii) has been revised and is being proposed as follows in § 348.50(c)(1)(iii): "If condition worsens, or if symptoms persist for more than 7 days or clear up and occur again within a few days, discontinue use of this product and consult a" (select one of the following: "physician" or "doctor"). (See comment 27 above.)

7. The indications for analgesic, anesthetic, and antipruritic ingredients and for counterirritant ingredients are proposed in § 348.50(b) to allow the optional use of terms describing the conditions relieved by these ingredients and to include the general claim "for the relief of itching" for antipruritic ingredients. To improve consumer understanding, the agency proposes deletion of the term "dermatitis" from the indications for hydrocortisone drug products, while it proposes to add "feminine itching." The agency is also proposing an optional indication for hydrocortisone drug products. (See comments 22, 27, 28, and 29 above.)

8. The agency is proposing the following warning in § 348.50(c)(7) for hydrocortisone products that are labeled with the optional indication of external genital or feminine itching: "Do not use if you have a vaginal discharge. Consult a" (select one of the following: "physician" or "doctor"). (See comment 27 above.)

9. To provide clearer and more specific information to consumers, the agency proposes to revise the Panel's recommended warning for counterirritants in § 348.50(c)(2)(ii) to state: "Do not bandage tightly." (See comment 31 above.)

10. The following are agency-initiated changes in the Panel's recommended monograph based on the format and style of recently published monographs:

a. Section 348.10(a) has been redesignated § 348.12, and § 348.10(b) has been redesignated § 348.10.

b. The agency has redesignated proposed Subpart D of the monograph as Subpart C, placing the labeling sections under Subpart C.

c. The definitions sections has been revised to include only those definitions considered necessary for this tentative final monograph. The definitions under age for "infant, child, and adult" and the term "cutaneous sensory receptor" were deleted because they are not used in the labeling proposed in the tentative final monograph. The definitions for "topical analgesic" and "topical anesthetic" were combined under a new definition "analgesic, anesthetic" because the actions of a topical analgesic and a topical anesthetic are similar, and no distinction is made in the proposed indications section. (See comment 24 above.) A definition for camphorated metacresol has been added because the complex has been included in the monograph. (See comment 13 above.)

d. The subgroups of active ingredients listed in §§ 348.10 and 348.12 have been identified with headings that are in accordance with the Panel's recommendations.

e. In an efffort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs to substitute the word "doctor" for "physician" in OTC drug monographs on the basis that the word "doctor" is more commonly used and better understood by consumers. Based on comments received to these proposals, the agency has determined that final monographs and other applicable OTC drug regulations will give manufacturers the option of using either the word "physician" or the word "doctor." This tentative final monograph proposes that option.

f. The Panel's recommended warning in § 348.50(c)(1)(iv) has been deleted, and the following statement has been included under the directions in proposed § 348.50(d): "Children under 2 years of age: consult a" (select one of the following: "physician" or "doctor").

11. The agency has reclassified methapyrilene hydrochloride from Category I to Category II as an OTC external analgesic ingredient. A tentative final rule for nighttime sleep-aid., published in the **Federal Register** of June 13, 1978 (43 FR 25544), proposed to place methapyrilene in Category II because of preliminary studies implicating this drug as a carcinogen, or a carcinogen synergist with nitrates, in rats. However, at that time, the studies were too preliminary to support a definitive finding of carcinogenicity for methapyrilene itself that would necessitate its immediate removal from all products in the OTC drug market.

On May 1, 1979, the agency received an interim report from the National Cancer Institute (NCI) regarding carcinogenicity studies performed with methapyrilene at the Frederick Cancer Research Center. The results of these studies have been published by Lijinsky, Reuber, and Blackwell (Ref. 1). The NIC interim report stated that methapyrilene is a potent carcinogen in rats and must be considered a potential carcinogen in man. FDA reviewed this report and concurred with its conclusions. Industry agreed to a request from the agency to recall all methapyrilene-containing products from the market voluntarily. On June 15, 1979, FDA issued a recall letter to all manufacturers holding an approved new drug application (NDA) for products containing methapyrilene. This voluntary recall has virtually eliminated drug products containing methapyrilene from the marketplace. All human drugs containing methapyrilene for systemic or topical use are currently regarded as new drugs within the meaning of section 201(p) of the act (21 U.S.C. 321(p) and are subject to regulatory action under sections 502 and 505 of the act (21 U.S.C. 352 and 355).

Reference

(1) Lijinsky, W., M. D. Reuber, and B. N. Blackwell, "Liver Tumors Induced in Rats by Chronic Oral Administration of the Common Antihistamine Methapyrilene Hydrochloride," *Science*, 209:817–819, 1980.

12. Thymol has been deleted from recommended § 348.20(b)(1)(ii) as an ingredient for inclusion in combinations of external analgesic active ingredients. The Panel classified thymol as Category III. Thymol was inadvertently included in the Panel's recommended nonograph. The agency tentatively concurs with the Panel's Category III classification of thymol and is correcting this error in the monograph.

13. The agency is proposing to lower the upper concentration limit for phenol and phenolate sodium from 2 percent to 1.5 percent in external analgesic drug products. Monographs for other OTC drug products for external use limit the concentration of phenol to 1.5 percent. for example, the tentative final monograph for OTC Antimicrobial I drug products classified concentrations of phenol exceeding 1.5 percent as Category II for safety when used in antimicrobial soaps, patient preoperative skin preparations, health-care personnel handwashes, skin antiseptics, skin wound cleansers, skin wound products, and surgical hand scrubs. The agency stated in this document that the use of phenol in concentrations of 2 percent or more has caused serious hazards, including gangrene, mummification, and even coma (January 6, 1978; 43 FR 1227). The Panel on OTC Dentifrices and Dental Care Drug Products also placed phenol in concentrations above 1.5 percent in Category II as an oral mucosal analgesic (May 25, 1982; 47 FR 22739). The upper concentration limit of phenolate sodium, the sodium salt of phenol, is also being lowered to 1.5 percent so that it has the same limit as phenol.

An exception to this upper limit of 1.5 percent phenol has been made for phenol when combined with camphor. The agency has proposed that 4.7 percent phenol may be safely combined with 10.8 percent camphor. (See comment 13 above.)

14. The agency proposes that the warning recommended by the Panel in § 348.50(c)(5) for products containing phenol pertains also to products containing phenolate sodium and camphorated metacresol, and has amended the tentative final monograph accordingly in § 348.50(c)(5). The agency notes that the Panel used slightly different wording in the warnings it recommended in § 348.50(c)(3), (5), and (6) to convey the same message. To prevent consumer confusion, the agency has proposed the same wording, where applicable, in the warning statements in these sections. The Language in these warnings is taken from a similar warning that the agency proposed for topical antimicrobial drug products in the **Federal Register** of July 9, 1982 (47 FR 29986).

15. The agency is proposing to classify camphorated metacresol as Category I for safety and effectiveness and is including a definition of camphorated metacresol in § 348.3(b)—(See comment 13 above.)

16. For ease of understanding by consumers, the agency proposes to revise the warning recommended by the Panel in § 348.50(c)(3)(ii) as follows: "This product stains skin and clothing yellow."

The agency advises that those parts of §§ 310.201(a) (19) and (23), 369.20 and 369.21 applicable to external analgesic drug products will be revoked at the time that this monograph becomes effective.

The agency has examined the economic consequences of this proposed rulemaking and has determined that it does not require either a Regulatory

Impact Analysis, as specified in Executive Order 12291, or a Regulatory Flexibility Analysis, as defined in the Regulatory Flexibility Act (Pub. L. 96-354).

Some external analgesic drug products may have to be reformulated to delete nonmonograph ingredients; however, there are a number of Category I ingredients available for reformulation. The agency believes that minimal testing of nonmonograph ingredients will be done because of the availability of other ingredients for reformulation. Manufacturers will have up to 12 months to revise their product labeling. In most cases, this will be done at the next printing so that minimal costs should be incurred. Thus, the impact of the proposed rule, if implemented, appears to be minimal. Therefore, the agency concludes that the proposed rule is not a major rule as defined in Executive Order 12291. Further, the agency certifies that the proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act.

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

The agency has carefully considered the potential environmental effects of this proposal and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement therefore will not be prepared. The agency's finding of no significant impact, and the evidence supporting this finding, is contained in an environmental assessment (under 21 CFR 25.31, proposed in the **Federal Register** of December 11, 1979; 44 FR 71742), which may be seen in the Dockets Management Branch, Food and Drug Administration.

List of Subjects in 21 CFR Part 348

OTC drugs: External analgesics.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 as revised (see 47 FR 16010; April 14, 1982)), it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended by adding new Part 348 to read as follows:

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

Subpart A—General Provisions

Sec.
348.1 Scope.
348.3 Definitions.

Subpart B—External Analgesic Active Ingredients

348.10 Analgesic, anesthetic, and antipruritic active ingredients.
348.12 Counterirritant active ingredients.
348.20 Permitted combinations of active ingredients.

Subpart C—Labeling

348.50 Labeling of external analgesic drug products.

Authority: Secs. 201 (p), 501, 502, 505, 701, 52 Stat. 1041-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—General Provisions

§ 348.1 Scope.

(a) An over-the-counter external analgesic drug product in a form suitable for topical administration is generally recognized as safe and effective and is not misbranded if it meets each condition in this part and each general condition established in § 330.1.

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

§ 348.3 Definitions.

As used in this part:

(a) *Analgesic, anesthetic.* A topically (externally) applied drug that relieves pain by depressing cutaneous sensory receptors.

(b) *Antipruritic.* A topically (externally) applied drug that relieves itching by depressing cutaneous sensory receptors.

(c) *Camphorated metacresol.* A complex consisting of camphor and metacresol combined in a ratio of 3 parts camphor to 1 part metacresol.

(d) *Counterirritant.* A topically (externally) applied drug that causes irritation or mild inflammation of the skin for the purpose of relieving pain in muscles, joints, or viscera distal to the site of application by stimulating cutaneous sensory receptors.

(e) *External analgesic.* A topically (externally) applied drug that has a topical analgesic, anesthetic, or antipruritic effect by depressing cutaneous sensory receptors, or that has a topical counterirritant effect by stimulating cutaneous sensory receptors.

Subpart B—Active Ingredients

§ 348.10 Analgesic, anesthetic, and antipruritic active ingredients.

The active ingredients of the product consist of any of the following, within the established concentration for each ingredient:

(a) *Amine and "caine"-type local anesthetics.*

(1) Bensocaine 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.

(11) Tetracaine hydrochloride 1 to 2 percent.

(b) *Alcohols and ketones.*

(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 in accordance with § 348.20(a)(4).

(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.

(10) Resorcinol 0.5 to 3 percent.

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(c) *Antihistamines.*
(1) Diphenhydramine hydrochloride 1 to 2 percent.
(2) Tripelennamine hydrochloride 0.5 to 2 percent.
(d) *Hydrocortisone preparations.*
(1) Hydrocortisone 0.25 to 0.5 percent.
(2) Hydrocortisone acetate 0.25 to 0.5 percent.

§ 348.12 Counterirritant active ingredients.

The active ingredients of the product consist of any of the following within the established concentration for each ingredient:
(a) *Irritants that producer redness*—(1) Allyl isothiocyanate 0.5 to 5 percent.
(2) Strong ammonia solution, diluted to contain 1 to 2.5 percent ammonia.
(3) Methyl salicylate 10 to 60 percent.
(4) Turpentine oil 6 to 50 percent.
(b) *Irritants that produce cooling sensation.*—(1) Camphor exceeding 3 percent to 11 percent.
(2) Menthol 1.25 to 16 percent.
(c) *Irritants that produce vasodilation.*—(1) Histamine dihydrochloride 0.025 to 0.10 percent.
(2) Methyl nicotinate 0.25 to 1 percent.
(d) *Irritants that do not produce redness.*—(1) Capsaicin 0.025 to 0.25 percent.
(2) Capsicum containing 0.025 to 0.25 percent capsaicin.
(3) Capsicum oleoresin containing 0.025 to 0.25 percent capsaicin.

§ 348.20 Premitted combinations of active ingredients.

(a) *Combinations of external analgesic active ingredients.*—(1) Any ingredient identified in § 348.10(a) may be combined with any ingredient identified in § 348.10(b).
(2) Any ingredient identified in § 348.10(b) may be combined with any ingredient in § 348.10(c).
(3) Any ingredient identified in § 348.10(b)(1), (5), (7), (9), and (10) may be combined with camphor and menthol identified in § 348.10(b)(2) and (6).
(4) Camphor and phenol indentified in § 348.10(b)(3) and (8) may be combined in a light mineral oil, USP vehicle.
(5) Any two, three, or four ingredients indentified in § 348.12 may be combined provided that the combination contains no more than one active ingredient from each group identified in § 348.12(a), (b), (c), and (d).
(6) Camphor identified in § 348.12(b)(1) may be combined with menthol identified in § 348.12(b)(2).
(7) Camphor and menthol identified in § 348.20(a)(6) may be combined with any one, two, or three ingredients identified in § 348.12 provided the combination contains no more than one ingredient from each group identified in § 348.12(a), (c), and (d).

(b) *Combingtions of external analgesic active ingredients and other active ingredients.*—(1) Any ingredient identified in § 348.10(a), (b), or (c), or any combination identified in paragraph (a)(i), (2), or (3) of this section may be combined with any generally recognized safe and effective skin protectant active ingredient or skin protectant combination identified in Part 347 provided the product is labeled for the concurrent symptoms.
(2) Any ingredient identified in § 348.10(a), (b), or (c) or any combination identified in paragraph (a)(1), (2), or (3) of this section may be combined with any generally recognized safe and effective topical antimicrobial active ingredient or topical antimicrobial combination identified in Part 333, Subpart A, provided the product is labeled for the concurrent symptoms.

Subpart C—Labeling

§ 348.50 Labeling of external analgesic drug products

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as follows:
(1) *For products containing any ingredient identified in § 348.10(a), (b), and (c) and § 348.12.* The labeling identifies the product as an "external analgesic," "topical analgesic," or "pain relieving (*insert dosage form, e.g., cream, lotion, or ointment*)."
(2) *For products containing hydrocortisone or hydrocortisone acetate identified in § 348.10(d).* The labeling identifies the products as "antipruritic (anti-itch)," "anti-itch." "antipruritic (anti-itch) (insert dosage form, e.g., cream, lotion, or ointment)," or "anti-itch (insert dosage form, e.g., cream, lotion, or ointment)."
(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indication(s)" that is limited to the following:
(1) *For products containing any external analgesic active ingredients identified in § 348.12.* "For the temporary relief of minor aches and pains of muscles and joints" [which may be followed by: "associated with" (select one or more of the following: "simple backache," "arthritis," "strains," "bruises," and "sprains."]]
(2) *For products containing any external analgesic active ingredients identified in § 348.10(a), (b), and (c).* "For the temporary relief of" (select one of the following: "pain," "itching," or "pain and itching") (which may be followed by: "associated with" (select one or more of the following: "minor burns," "sunburn," "minor cuts," "scrapes," "insect bites," or "minor skin irritations.")]
(3) *For products containing any external analgesic active ingredients identified in § 348.10(d).* The labeling of the product contains one of the following indications: (i) "For the temporary relief of itching associated with minor skin irritations and rashes" [which may be followed by: "due to" (select one or more of the following: "eczema," "insect bites," "poison ivy, poison oak, or poison sumac," "soaps," "detergents," "cosmetics," "jewelry,") and/or ("and for external" (select one or more of the following: "genital," "feminine," and "anal") "itching.")]
(ii) "For the temporary relief of itching associated with minor skin irritations, inflammation, and rashes due to" (select one or more of the following: "eczema," "insect bites," "poison ivy, poison oak, poison sumac," "soaps," "detergents," "cosmetics," and "jewelry") (which may be followed by: "and for external" (select one or more of the following: "genital," "feminine," and "anal") "itching.")
(4) *Other allowable statments.* In addition to the required information specified in this paragraph and in paragraphs (a), (b), (c), and (d) of this section, the labeling of the product may contain any of the following statements, as appropriate for the product's formulation, provided such statements are neither placed in direct conjuction with information required to appear in the labeling nor occupy labeling space with greater prominence or conspicuousness than the required information.
(i) *For products containing any ingredient identified in § 348.12.*
(*a*) (optional: "provides") "penetrating pain relief."
(*b*) (optional: "provides") "warming pain relief."
(*c*) (optional: "provides") "cooling pain relief."
(ii) [Reserved]
(c) *Warnings.* The labeling of the product contains the following statements under the heading "Warnings."
(1) *For products containing any external analgesic active ingredient identified in §§ 348.10 and 348.12.* (i) "For external use only."
(ii) "Avoid contact with the eyes."
(iii) "If condition worsens, or if symptoms persist for more than 7 days or clear up and occur again within a few days, discontinue use of this product and consult a" (select one of the following: "physician" or "doctor").

(2) *For products containing any external analgesic active ingredient identified in §348.12.* (i) "Do not apply to wounds or damaged skin."

(ii) "Do not bandage tightly."

(3) *For products containing butamben picrate identified in §348.10(a)(2).* (i) "Do not apply over large areas of the body."

(ii) "This product stains skin and clothing yellow."

(4) *For products containing any external analgesic active ingredient identified in §348.10(a)(3), (4), (7), (8), (10), and (11).* "Do not use in large quantities, particularly over raw surfaces or blistered areas."

(5) *For products containing camphorated metacresol identified in §348.10(b)(4), phenol identified in §348.10(b)(7) and (8), and phenolate sodium identified in §348.10(b)(9).* "Do not apply over large areas of the body or bandage."

(6) *For products containing resorcinol identified in §348.10(b)(10).* "Do not apply over large areas of the body."

(7) *For products containing hydrocortisone preparations identified in §348.10(d) (1) and (2) that are labeled with the indications "* * * for external genital itching," or "* * * for external feminine itching."* "Do not use if you have a vaginal discharge. Consult a" (select one of the following: "physician" or "doctor").

(d) *Directions.* The labeling of the product contains the following statement under the heading "Directions": *Adults and children 2 years of age and older:* Apply to affected area not more than 3 to 4 times daily. Children under 2 years of age: consult a (select one of the following: physician or doctor).

Interested persons may, on or before April 11, 1983 submit to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before June 8, 1983. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register.**

Interested persons, on or before February 8, 1984 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 9, 1984. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA-305) (address above). Received data and comments may also be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on April 9, 1984. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register** unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Dated: January 19, 1983.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Richard S. Schweiker,

Secretary of Health and Human Services.

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