

FDA Concurrence with the Recommendation of the Topical Analgesics Panel

48 FR 5852 at 5865 - 5869

February 8, 1983

FDA agreed with the Topical Analgesics (Advisory Review) Panel recommendation that hydrocortisone and hydrocortisone acetate be considered safe and effective as OTC antipruritic active ingredients. Both the panel and FDA classified hydrocortisone and hydrocortisone acetate as Category I (safe and effective) active ingredients. Attached is an excerpt from volume 48 of the Federal Register which summarizes FDA's position with respect to the Topical Analgesics Panel's recommendations. The excerpt includes Part 348 of the Code of Federal Regulations listing hydrocortisone and hydrocortisone acetate, 0.25 to 0.5 percent, as active ingredients (21 CFR 348.10(d)(1) and (d)(2)) and defining appropriate labeling (21 CFR 348.50).

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.

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

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

Counterirritant ingredients	Panel	Agency
Allyl isothiocyanate	II	II
Strong ammonia solution ¹	II	II
Camphor	II	II
Capsaicin	II	II
Capsicum	II	II

Counterirritant ingredients	Panel	Agency
Capsicum oleoresin	II	II
Chloral hydrate	II	II
Eucalyptus oil	II	II
Histamine dihydrochloride	II	II
Menthol	II	II
Methyl nicotinate	II	II
Methyl salicylate	II	II
Turpentine oil	II	II

¹Identified 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 effort 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 monograph. 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) Phenol's sodium 0.5 to 1.5 percent.

(10) Resorcinol 0.5 to 3 percent.

(c) Antihistamines.

- (1) Diphenhydramine hydrochloride 1 to 2 percent.
- (2) Tripeleminamine 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 produce 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 Permitted 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 identified in § 348.10(b)(3) and (8) may be combined in a light mineral oil, USP vehicle.

(5) Any two, three, or four ingredients identified 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) *Combinations 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," "sprains," "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 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, as appropriate for the product's formulation, 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") "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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