DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 347

[Docket No. 78N-0021]

Skin Protectant Drug Products for Over-the-Counter Human Use; 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) skin protectant 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 of 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 requests for oral hearing before the Commissioner of Food and Drugs on the proposed regulation by April 18, 1983. New data by February 15, 1984.

Comments on the new data by April 16, 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). Comments on the agency's economic impact determination by June 15, 1983.

ADDRESS: Written comments, objections, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857. 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 (HFN-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of August 4, 1978 (43 FR 3468) 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 skin protectant 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 November 2, 1978. Reply comments in response to comments filed in the initial comment period could be submitted by December 4, 1978.

In a notice published in the **Federal Register** of March 21, 1980 (45 FR 18402), the agency advised that it had reopened the administrative record for OTC skin protectant drug products to allow for consideration of data and information that had been filed in the Dockets Management Branch after the date the administrative record previously had officially closed. The agency concluded that any new data and information filed prior to March 21, 1980, should be available to the agency in developing a proposed regulation 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 on the Dockets Management Branch (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information.

The advance notice of proposed rulemaking, which was published in the **Federal Register** on August 4, 1978 (43 FR 34628), 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) the FDA states for the first time its position on the establishment of a monograph for OTC skin protectant 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 monograph for OTC skin protectant drug products.

In response to the advance notice of proposed rulemaking, 1 drug manufacturers' association, 1 cosmetic manufacturers' association, and 12 drug and cosmetic manufacturers submitted comments. Copies of these comments are on public display in the Dockets Management Branch.

This proposal would amend Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations by adding new Part 347. This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC skin protectant 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 or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph (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 tenative 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 skin protectant drug products (published in the **Federal Register** of August 4, 1978 (43 FR 34628)), 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 will 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 reformulate their products and have them 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 December 12, 1972 (37 FR 26456) or to additional information that has come to the agency's attention since publication of 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 39436), FDA issued a notice of reopening of the administrative record for OTC skin protectant drug products to allow for consideration of the Miscellaneous External Panel's recommendations on skin protectant drug products used for the treatment of diaper rash, for prevention of poison ivy, oak, and sumac, for the treatment of fever blisters, as astringents, and as insect bity neutralizers. The agency will address the use of skin protectant 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 Skin Protectant drug Products

1. Several comments 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, publishd 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. Two comments requested withdrawal of the advance notice of proposed rulemaking and initiation of a new rulemaking, while another comment urged that Panel deliberations be reopened, to allow cosmetic manufacturers an opportunity to present their positions. The comments contended that the cosmetic industry was not provided enough notice and a fair opportunity to participate in the rulemaking. The comments argued that the call-for-data notice (December 12, 1972; 37 Fr 26456) did not mention cosmetics and that the agency has stated that any product for which only cosmetic claims are made, and which is therefore not a drug, will not be reviewed.

The agency regularly published notices in the **Federal Register** announcing the dates of the Panel's meetings, part of each meeting was open to the public, and minutes of each meeting were publicly available. One of the industry lisison members to the Panel was nominated by the Cosmetic, Toiletry, and Fragrance Association (CTFA). For these reasons, the agency believes that adequate opportunity was provided for all parties, including cosmetic manufacturers, to present their positions to the Panel. Because the Panel has been disbanded, its deliberations cannot be reopened. The agency believes that no valid basis exists to withdraw the advance notice of proposed rulemaking and to initiate a new rulemaking. Ample opportunities have existed and continue to exist for all interested persons to express their opinions before the agency reaches any final conclusions on OTC skin protectant drug products. For example, interested persons, including cosmetic manufacturers, could comment and submit data during the comment period following publication of the Panel's report and may do so again following publication of this tentative final monograph. (For a discussion of the distinction between the drug and cosmetic use of these ingredients, see comment 6 below.)

3. One comment requested an extension of time for filing comments to the advance notice of proposed rulemaking for OTC skin protectant drug products in order to compare it with the advance notice of proposed rulemaking on OTC anorectal drug products, which

had not been published at the time the comment was submitted. the comment was submitted by a manufacturer concerned that the labeling and other portions of the two rulemakings would overlap with respect to white petrolatum, an ingredient contained in a marketed product submitted to both rulemakings.

The agency points out that, subsequent to the comment's request, the advance notice of proposed rulemaking for anorectal drug products was published in the **Federal Register** of May 27, 1980 (45 FR 35576), and comments were submitted to that rulemaking by the originator of the comment above. Additional comments may be filed for 60 days following publication of this tentative final monograph. Thus, ample opportunity is being provided through the normal OTC drug review procedures for comment on the handling of white petrolatum in the rulemakings for skin protectant and anorectal drug products.

4. One comment pointed out a discrepancy on pages 34628 and 34629 of the panel's report (43 FR 34628–34629). The comment noted that on page 34628 the report indicates that a request was made for data and information on all active ingredients utilized in topical analgesic products, including antirheumatic, otic, burn, and sunburn treatment and prevention drug products, while on page 34629 the report indicates that a request was made for data and information on OTC skin protectant drug products.

The comment is correct. On page 34628, reference is made to the notice issued in the **Federal Register** of December 12, 1972 (37 FR 26456), which contained a request for data and information on all active ingredients utilized in topical analgesic, including antirheumatic, otic, burn, and sunburn treatment and prevention drug products. Subsequent to the 1972 request for data, the Panel organized the active ingredients in this broad listing of ingredients into four major pharmacologic groups, external analgesics, skin protectants, topical otics, and sunscreens, and prepared a report on each. The statement on page 34629 was made in reference to data and information on skin protectants received in response to the December 12, 1972 notice.

5. One comment complained that many of the products and ingredients in the list of submissions to the Panel (43 FR 34629) come within the scope of the broad category of topical analgesics rather than the more narrow category of skin protectants. The comment maintained that placing an ingredient in Category II on the basis of this narrow range of use, and what it alleged to be a restricted literature search of skin protectant drugs, stigmatized the ingredient as unsafe and ineffective for other uses. Citing sulfur as an example, the comment contended that its Category II classification as a skin protectant could result in bias by other OTC panels evaluating sulfur for other uses. The comment mentioned three references to support the effectiveness of sulfur for different topical uses and argued that it should be evaluated for these uses in appropriate rulemakings (Refs. 1, 2, and 3).

The agency acknowledges that many of the products and ingredients identified in the Panel's report (43 FR 34629) have uses other than as skin protectants. As stated at 43 FR 34630, the Panel considered a number of these ingredients in its sunscreen and external analgesic reports, and not in the skin protectant report. The Panel's Category II classification of sulfur for safety as a skin protectant did not influence other panels to place sulfur in Category II for other uses. For example, sulfur was subsequently classified in Category I by the Miscellaneous External Panel for use in controlling dandruff and by the Antimicrobial II Panel for treatment of acne. The agency believes these Category I classifications of sulfur demonstrate the impartial consideration of ingredients for their different OTC uses under appropriate rulemakings.

References

(1) Harvey, S. C., "Antiseptics and Disinfectants; Fungicides; Ectoparasiticides," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, The MacMillan Co., New York, p. 1005, 1975.

(2) "The Dispensatory of the United States of America," 25th Ed., edited by A. Osol and G. E. Farrar, Jr., J. B. Lippincott Co., Philadelphia, pp. 1368–1373, 1955.

(3) "AMA Drug Evaluations," 3d Ed., American Medical Association, Publishing Sciences Group, Inc., Littleton, MA, pp. 915–916, 1977.

6. Numerous comments pointed out that many of the ingredients included in the skin protectant monograph as active ingredients have historically been used in cosmetic products. The comments questioned the scope of the monograph, contending that it cannot be used to regulate cosmetic products that are not represented for use as drugs because whether a product is a drug or a cosmetic is determined by the vendor's representations in labeling or advertising. To support their contention, some comments cited definitions of "drug" and "cosmetic" in section 201 (g) and (i) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321 (g) and (i)), FDA Trade Correspondence issued in 1940, and prior case law. Some comments recommended revising the scope, definition, and indications sections of the monograph to emphasize that it regulates drugs only, and to state explicitly that it excludes cosmetics. Several comments requested the agency to clarify that the concentration range limitations and warnings established in the monograph do not apply to the use of the same ingredients in cosmetic products.

The agency agrees that this monograph applies only to skin protectant products that fall within the statutory definition of "drugs." The act principally defines a "drug" as an article "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" or "intended to affect the structure or function of the body * * *." (21 U.S.C. 321(g)(1)(B), (C)). A "cosmetic," on the other hand, is defined primarily as an article intended to be "applied to the human body * * * for cleansing, beautifying, promoting attractiveness, or altering the appearance" (21 U.S.C. 321(i)(1)). The intended use of a product, therefore, determines whether the product is a "drug," a "cosmetic," or both. This intended use may be inferred from the product's labeling, promotional material, advertising, and any other relevant factor. See, e.g., *National Nutritional Foods Ass'n* v. *Mathews*, 557 F. 2d 325, 334 (2d Cir. 1977). In order to make it clear that the scope of the monograph extends only to drug products, the agency is proposing the following changes in this tentative final monograph: The word "drug" is being added to § 347.1 ("*Scope*"), to read "An over-the-counter skin protectant drug product * * *." The word "drug" is being substituted for "agent" in the definition of "skin protectant" in § 347.3, to read "*Skin protectant.* A drug which * * *." (See also comment 7 below.)

Because the final monograph will cover only the drug use of the active ingredients listed therein, the concentration range, limitations, warnings, and directions established for these ingredients in the monograph will not apply to the use of the same ingredients in products intended solely as cosmetics. Those products intended for both drug and cosmetic use must conform to the requirements of the final monograph. However, in addition to the indications allowed for skin protectant drug products, such products may also bear appropriate labeling for cosmetic uses, in conformity with section 602 of the act (21 U.S.C. 362) and the provisions

of 21 CFR Part 701. Consistent with the provisions of § 701.3(d) (21 CFR 701.3(d)) regarding label declarations of active drug ingredients and cosmetic ingredients, it is the agency's view that cosmetic claims appearing in any portion of the labeling that is required by the monograph could be misleading. Cosmetic claims may appear elsewhere in the labeling.

7. Several comments requested that the Panel's definition of a skin protectant in § 347.3 ("* * * an agent which isolates the exposed skin or mucous membrane surface from harmful or annoying stimuli") be revised. The comments contended that the definition was too broad and could be applied to both drugs and cosmetics; that, to limit its scope to drug products, the word "drug" or "OTC drug" should be substituted for the word "agent" and that the word "exposed" should be changed to "injured or damaged."

As discussed in comment 6 above, the agency has clarified that this mongraph applies only to drug products, and the word "agent" in the definition of a skin protectant has been changed to "drug." The agency agrees that the words "injured or damaged" could be added to the definition to describe the condition of the skin being treated. However, the word "exposed" also describes the drug use of the product when it is used for prevention purposes, such as to prevent chafing or windburn. Therefore, the agency concludes that both conditions are appropriate in the definition of a skin protectant. In addition, the agency believes that the word "protects" better describes the action of these products than the word "isolates." Thus, the definition of a skin protectant has been revised to read "* * * a drug which protects injured or exposed skin or mucous membrane surface from harmful or annoying stimuli."

B. Comments on Skin Protectant Ingredients

8. One comment requested that the skin protectant monograph not be finalized until the OTC Miscellaneous External Panel completed its review of glycerin. The comment contended that the call for data for topical analgesic drug products (37 FR 26456; December 12, 1972) did not include the indications of dry skin, minor skin irritation, skin protectant, or chapping; that glycerin was listed in the call for data for OTC miscellaneous external drug products (40 FR 38179; August 27, 1975); and that the Miscellaneous External Panel received data on the effectiveness of 2 percent glycerin in relieving dry skin.

Glycerin was labeled as an ingredient in marketed products submitted to the Topical Analgesic Panel. The Panel reviewed the data submitted to it on glycerin and classified it as a Category I skin protectant, even though the Miscellaneous External Panel's call for data listed that ingredient and those indications while the Topical Analgesic Panel's call for data did not.

The Miscellaneous External Panel completed its work on December 15, 1980, and did not review the submission on 2 percent glycerin submitted to it. The agency has determined that all data not reviewed by the Miscellaneous External Panel will be incorporated into the appropriate rulemakings and reviewed by the agency. Accordingly, the submission on 2 percent glycerin and other skin protectant submissions not reviewed by the Miscellaneous External Panel will be incorporated into the administrative record for skin protectant drug products at a later date. The skin protectant final monograph will not be issued until these data have been reviewed by the agency and interested persons provided an opportunity to comment on an agency proposal.

9. One comment submitted two journal articles to support the effectiveness of glycerin as a skin protectant at aqueous concentrations lower than the 20 to 45 percent recommended by the Panel (Refs. 1 and 2). The comment contended that effectiveness had been shown in one of these studies with a product containing 14 percent glycerin and requested that the allowable concentration range for glycerin be lowered to 14 percent.

The agency has reviewed the two articles submitted by the comment and concludes that the studies are not sufficient to demonstrate the effective use of glycerin at concentrations lower than those recommended by the Panel. The study by Johnson (Ref. 1) was an open clinical evaluation designed to show effectiveness in treating many common dermatoses, such as eczema, xeroderma, and dermatitis. The article reports that the test product used to treat all patients was a cream consisting basically of dimethicone 2.5 percent (a Category I skin protectant) in a hydrophilic base. The comment states that the product also contained 14 percent glycerin; however, there is no mention of glycerin in the article, and therefore any effects obtained cannot be attributed to glycerin.

The study by Harb (Ref. 2) measured the ability of 1,3-butylene glycol and glycerin at concentration levels of 5, 10, or 20 percent to retard water vapor loss when added to skin cream formulations (water-in-oil and oil-in-water emulsions), compared with the same cream formulations without 1,3-butylene glycol or glycerin. While glycerin appeared to prevent some water vapor loss from these preparations when tested in vitro, no information was provided on how the results of this study are applicable to an in vivo situation.

The agency finds that these journal articles do not support the effectiveness of glycerin as a skin protectant ingredient at concentrations lower than 20 percent, as the comment contended. The agency notes that the Advisory Review Panel on OTC Hemorrhoidal Drug Products (hereinafter referred to as the Hemorrhoidal Panel) also found 20 to 45 percent glycerin to be effective as a protectant (in OTC anorectal preparations) (45 FR 35630). Therefore, the agency concludes that 20 to 45 percent glycerin is the suitable range for use as an OTC skin protectant.

References

(1) Johnson, A., "Non-Steroid Skin Cream in Traumatic Dermatoses: A Clinical Open Evaluation," *Medical Journal of Australia*, 1:111–113, 1976.

(2) Harb, N. A., "1,3-Butylene Glycol as a Humectant in Cosmetic Creams," *Drug and Cosmetic Industry*, 115:48–60, 1974.

10. One comment requested a change in the Panel's statement that live yeast cell derivative is "obtained by refluxing cakes of live yeast with ethanol" (43 FR 34645). The comment stated that in its general discussion the Panel did not specify use of yeast cakes and that both cakes and moist yeast may be used. The comment requested that the word "cakes" be deleted from the Panel's statement.

The agency agrees withe the comment that live yeast cell derivative may be obtained from both compressed (caked) and moist forms of the live yeast *Saccharomyces cerevisiae* and that a more accurate statement would be "* * * may be obtainted by refluxing live yeast with ethanol."

11. One comment urged that live yeast cell derivative be placed in Category I as a wound-healing aid. The comment contended that sufficient data to demonstrate efficacy were submitted to the Panel, but the Panel did not consider as adequate the evidence that live yeast cell derivative by itself increases collagen formation in vivo. The comment further indicated that data were being developed to respond to questions raised by the Panel about wound healing agents and had requested that it be permitted to present these data for the Panel's consideration. However, the comment was unaware that the Topical Analgesic Panel had signed off on its final report on skin

protectants at its December 1977 meeting. Therefore, the comment provided clarification of the data which had previously been submitted to the Panel and additional data which the Panel had not had an opportunity to consider.

The comment noted that the Panel had characterized the various in vitro and in vivo data as "sophisticated." It is well accepted that collagen formation is the central event of the biological repair process and the accepted indicator of newly formed collagen is the conversion of proline to hydroxyproline measured by the presence of radioactive hydroxyporline. The comment noted that the Panel stated that "collagen production and cross linkages have been experimentally quantified by measurements of collagen production and wound tensile strength * * *. Most agents promoting experimental wound healing such as oxygen, oral ascorbic acid, and oral vitamin A, appear to act primarily to promote collagen synthesis." (See 43 FR 34631.) The comment contended that the Panel had not taken into consideration the evidence presented that live yeast cell derivative alone increases collagen formation. The Panel had indicated that there was a significant increase in the mean net weight of new tissue and in hydroxyproline content in the in vivo study in rats and an average increase of C^{14} labeled proline uptake of 70 percent in incubated human skin samples. Instead, the Panel conclude that "it has duly noted that the manufacturer's data show that live yeast cell derivative alone is responsible for the increased oxygen uptake by skin treated with the whole product (live yeast cell derivative and shark liver oil)." The comment stated that the Panel ignored the series of sophisticated experiments it had itself described using human skin tags in vitro and implanted cylinders in vivo which clearly demonstrate a significant increase in collagen formation.

The comment also stated that several studies were reviewed by the Hemorrhoidal Panel. That Panel was divided in its findings with regard to the data. The majority of the Panel (four members) was concerned that efficacy needed to be demonstrated in the anorectal area and did not accept data in other areas. A minority of the Panel (three members) believed the data warranted a finding of Category I for live yeast cell derivative as a wound healing agent. The comment noted that experts in the field were also consulted and concluded that the data for live yeast cell derivative are adequate for safe and effective use as a wound healing agent.

In summary, the comment maintained that the most rigorous testing within technical capability of a wound healing research laboratory had been met for live yeast cell derivative and that experts in wound healing concluded that there was more than enough evidence to establish that live yeast cell derivative is effective as a wound healing agent. In addition, these tests have shown that live yeast cell derivative acts independently of the combination of live yeast cell derivative and vitamin A as a wound healing agent.

The agency has carefully reviewed the "clarifications" contained in the comment with regard to the studies evaluated by the Topical Analgesic Panel and has evaluated the additional data not reviewed by the Panel.

The additional data compared the effects of vitamin A, live yeast cell derivative, and a combination of these active ingredients on collagen synthesis by studying the incorporation of proline into hydroxyproline in human skin slices obtained from surgical procedures. Skin samples from two separate sources were incubated in the presence of C^{14} labeled proline, after which the skin was separated from the medium and the amount of hydroxyproline formed was measured by isotope counting techniques. The results indicate that vitamin A alone increased collagen formation by 57 percent and live yeast cell derivative by 122 percent, whereas the combination of vitamin A and live yeast cell derivative increased collagen formation by 112 percent. The agency has reviewed these data and concludes that live yeast cell derivative alone may promote collagenous repair. The agency concurs with the Panel that submitted animal and in vitro studies support a positive influence of live yeast cell derivative on wound healing. Specifically, live yeast cell derivative has the characteristic of a wound healing aid, i.e., increased oxygen uptake, hydroxyproline formation which is associated with collagen byosynthesis, tissue growth, and epithelization.

The majority of the Hemorrhoidal Panel had concluded that there was insufficient evidence to prove the safety and effectiveness of live yeast cell derivative as a wound healing agent for use in the anorectal area. The Panel noted that no studies of safety of live yeast cell derivative have been specifically carried out, although no toxicity has been noted when the compound was used in experimental animals and no reports of clinical toxicity have been made or noted in the various clinical studies of the commercial product containing live yeast cell derivative. The Panel therefore assumed that the compound is safe for limited use (1 week or less). The minority of the Hemorrhoidal Panel disagreed and concluded that live yeast cell derivative should be placed in Category I as safe and effective. Whereas the agency has not fully evaluated the use of live yeast cell derivative in the anorectal area, it concurs with the Topical Analgesic Panel's conclusion that the ingredient is safe for use as a wound healing agent for minor cuts, scrapes, and burns. The use of live yeast cell derivative for the relief of symptoms in the anorectal area will be addressed in the rulemaking for OTC anorectal drug products at a later date in a future issue of the **Federal Register.**

Even though the ingredient can be considered safe for use as a wound healing agent, there remains a lack of sufficient data on its effectiveness. Corroborations of the effects of live yeast cell derivative on wound healing of the type proposed for OTC use in human subjects in a well-controlled clinical study are still unavailable. Clarifications were provided in the comment regarding one human study reviewed by the Panel involving donor wound sites in patients with burn wounds, including the fact that each patient acted as his own control and often several donor sites were used for control measurements on the same patient (Ref. 1). However, even with these data, the agency concurs with the Panel's conclusion that the study remains insufficient to demonstrate a clinically significant effect. The study can only be considered as suggesting a potential wound healing effect. The number of patients is too small and the data too subjective to arrive at a conclusive interpretation.

The comment also referred to two human clinical studies in the literature that were not addressed by the Panel. In a 1944 study, Barnes (Ref. 2) evaluated the healing rate of human skin determined by the measurement of the electrical potential on experimental abrasions. The rate of healing was measured objectively by a recording potentiometer to avoid the subjective attempt to measure visually ill-defined areas of healing with photographs. After the normal potential differences between homologous digits on each hand were measured, the left fingers were sterilized with alcohol and the tips of four fingers were marked with sterilized sandpaper until blood

appeared. The electrical potential of the fresh wound was measured as the difference between an injured left finger and the intact homologous right finger. Following measurement of the wound's electrical potential, two fingers were treated with live yeast cell derivative combined with non-saponified liver oil. The other two fingers were treated with petrolatum as controls. Barnes concluded that the live yeast cell derivative-containing product accelerates healing on human skin to statistically significant degrees compared with control abrasions treated with petrolatum alone. The agency has reviewed the article and believes that it provides supportive evidence. However, the article does not provide conclusive evidence of effectiveness for OTC uses. Measurement of electrical potential has not been validated as a reliable indicator of wound healing. In addition, live yeast cell derivative as a single ingredient was not evaluated. In the second study referred to in the comment, Walsh and Nutini (Ref. 3) reported in 1943 on burn therapy founded on cellular stimulation. The article summarizes 100 burn cases treated with a live yeast cell derivative-containing product. The agency has reviewed the findings and concludes that the article lacks sufficient information to establish effectiveness for OTC uses. Live yeast cell derivative was not used alone and only 3 of the 100 burn patients were discussed.

In conclusion, the agency agrees that the available data suggest a positive influence on wound healing, but live yeast cell derivative has not been evaluated in an adequate well-controlled study in conditions such as minor cuts, scrapes, and burns, that would represent the symptoms most often to be treated OTC. The agency concurs with the Panel's evaluation that there is inadequate proof of effectiveness of live yeast cell derivative. The agency's detailed comments and evaluations on the data are on file with the Dockets Management Branch (Ref. 4). The agency recommends that the study design for any clinical evaluation of the effectiveness of live yeast cell derivative be prepared in consultation with FDA. The procedures for consulting about proposed protocols are described in a policy statement published in the **Federal Register** on September 29, 1981 (46 FR 47740).

References

(1) Trunkey, D., "Effectiveness of SRF on Donor Wound Sites," draft of unpublished paper in OTC Volume 060160.

(2) Barnes, T. C., "Healing Rate of Human Skin Determined by Measurement of the Electrical Potential of Experimental Abrasions," *The American Journal of Surgery*, 69:82–88, 1945.

(3) Walsh, T. P., and L. G. Nutini, "Burn Therapy Founded on Cellular Stimulation," *Southern Medicine and Surgery*, 104:143–152, 1943.

(4) Letter from W. E. Gilbertson, FDA, to S. F. Barshay, Whitehall Laboratories, coded LET, Docket No. 78N–0021, Dockets Management Branch.

12. One comment objected to the Panel's recommendation against using shark liver oil and live yeast cell derivative on children under 2 years of age without consulting a physician. The comment contended that both ingredients are safe and effective as skin protectants for use on children under 2 years of age for treatment of diaper rash. The comment cited Grayzel, Heimer, and Grayzel (Ref. 1) in support of the safety of topical application of cod liver oil and the "Handbook of Nonprescription Drugs" (Ref. 2) in support of the use of shark liver oil and cod liver oil as sources of vitamins A and D in the treatment of diaper rash. The comment argued that the Panel gave no reason for limiting the use of shark liver oil and live yeast cell derivative on children under 2, and failed to mention that a product containing both shark liver oil and live yeast cell derivative was submitted specifically for diaper rash (Ref. 3).

The agency notes that the product referred to by the comment is listed at 43 FR 34629 as one of the marketed products submitted to the Panel. The agency has reviewed the Panel's report and notes that the Panel discussed shark liver oil and live yeast cell derivative for use as skin protectant ingredients only. The product referred to by the comment was also submitted to the Miscellaneous External Panel and was reviewed by that Panel for diaper rash claims (Ref. 4).

The administrative record for the skin protectant rulemaking was reopened on September 7, 1982 (47 FR 39436) to include the recommendations of the Miscellaneous External Panel on drug products used for the treatment of diaper rash. The agency will review the submission on the product containing shark liver oil and live yeast cell derivative for use as skin protectants and for the treatment of diaper rash as part of its evaluation of these drug products. The agency notes that the references submitted by the comment do not address the question of systemic absorption of vitamins A and D across infant skin, although Grayzel, Heimer, and Grayzel (Ref. 1) discuss local absorption by epithelial cells and attribute the safety of cod liver oil to lack of evidence of sensitivity or dermatitis. The agency will consider this reference as part of its evaluation of diaper rash drug products. Until that evaluation has been completed, the agency will defer a decision on limiting the use of shark liver oil and live yeast cell derivative for use as skin protectants and for the treatment of diaper rash on children under 2 years of age. The agency invites the submission of additional data on these uses of shark liver oil, particularly on children under 2 years of age.

References

(1) Grayzel, H., C. Heimer, and R. Grayzel, "The Value of a Cod Liver Oil Ointment and Cod Liver Oil Lotion in the Treatment of Dermatoses," *New York State Journal of Medicine*, 53:2233–2237, 1953.

(2) Smith, G., "Handbook of Non-prescription Drugs," 5th Ed., American Pharmaceutical Association, Washington, p. 354, 1977.

(3) OTC Volume 060113.

(4) OTC Volume 160271.

13. One comment objected to the Panel's Category II classification for tannic acid. The comment argued that the Panel discussed only unsafe concentrations (e.g., 10 to 20 percent) and unsafe uses (e.g., use on severe burns and injection into animals). The comment stated that the Panel's discussion was not applicable to its product, which contains 3.92 percent tannic acid and is intended for minor burns only. Further, the comment contended that using 2 or 3 sprays of its product (each containing 50 mg of tannic acid) is not dangerous, and even if the entire bottle (90 sprays) were used on a minor burn, the 4.44 g of tannic acid applied would not be harmful. The comment added that tannic acid spray is intended for use for immediate applicatin by consumers as first aid in first and second degree burns and is not intended for use by physicians in a burn center for excessive skin damage. The comment contended that its 3.92 percent tannic acid spray treatment for burns forms a light covering or film, rather than a crust as the Panel stated (43 FR 34644), and maintained that this film reduces the likelihood of bacterial growth.

The agency concurs with the Panel's Category II classification of tannic acid as a skin protectant for the treatment of burns. The data cited by the Panel have shown that tannic acid in varying concentrations is absorbed when applied topically to severe burns. The agency does not have data demonstrating that tannic acid in concentrations as low as 3.92 percent

applied topically to minor burns would not be absorbed, nor did the comment present any. The film or crust formed over abraded tissue provides a suitable medium under which bacterial growth may flourish. The agency concurs with the Panel's conclusion that tannic acid is not safe or effective for burn therapy and is not suitable as an OTC skin protectant.

14. One comment contended that the 80- to 100-percent concentration range for cocoa butter in skin protectant products is unnecessarily high. The comment stated that because cocoa butter is a rather hard solid at room temperature, it would be difficult, if not impossible, for lotion and soft ointment formulations to contain cocoa butter even at the proposed lower level of 80 percent. The comment stated its understanding that the Hemorrhoidal Panel was recommending the use of cocoa butter as a protectant for use in the anorectal area at not less than 50 percent levels and requested that the agency lower the concentration of cocoa butter to 50 percent in the skin protectant rulemaking. The comment added that this lower percentage would permit the same level of skin protectant efficacy as the higher concentrations.

The Panel's recommended dosages for cocoa butter as a skin protectant were based on clinical and marketing experience of the products reviewed. The Panel noted that, due to its bland nonirritating properties, cocoa butter is used as a protectant on abraded or irritated tissue, especially in the anorectal area (45 FR 35630). The Hemorrhoidal Panel concluded that cocoa butter is safe and effective as a protectant in OTC preparation in concentrations of at least 50 percent (45 FR 35629). In view of those findings, the agency agrees with the comment and is proposing a dosage range for cocoa butter from 50 to 100 percent for use as an OTC skin protectant.

15. One comment requested that the concentration range of 10 to 85 percent recommended by the Panel for corn starch be extended to 10 to 100 percent. The comment stated that there was no medical reason for the upper concentration of corn starch to be limited to 85 percent and that this limit was based on the highest concentration of corn starch contained in a commercially available product submitted to the Panel. The comment mentioned that its own product contains 96 to 97 percent corn starch and that the directions for use recommended by the Panel (i.e., to use on adults, children, and infants liberally as needed) support raising the upper concentration limit.

The Panel recognized that corn starch has an effective absorptive capacity for moisture and is likely to form a sticky mass if used alone (i.e., at 100 percent) on the skin (Ref. 1). The Panel also noted that the incorporation of a finely dispersed dessicant in a formulation may eliminate this undesirable effect of corn starch. In light of the wide use of corn starch and because there is no reason to question the safety of corn starch when used externally, the agency tentatively agrees with the comment that the upper concentration limit for corn starch could be raised. However, the agency believes that an increase to a concentration of 97 percent, rather than 100 percent, would be appropriate to allow for formulation with a dessicant or other pharmaceutical necessity. As discussed in comment 22 below, the agency is tentatively deleting corn starch from the skin protectant monograph until diaper rash drug products are reviewed. The agency will state its proposal on the appropriate upper concentration limit for corn starch at that time.

Reference

(1) Barnett, G. "Baby Toiletries," *in* "Cosmetics Science and Technology," 2d Ed., edited by M. S. Balsam and E. Saqarin, Wiley-Interscience, New York, 1:154, 1972.

16. One comment requested that concentrations of zinc oxide up to and including 40 percent be permitted for OTC skin protectant drug products. The comment stated its belief that the Panel had limited the upper concentration of zinc oxide to 25 percent because it did not receive any data to substantiate the use of this ingredient at higher concentrations. The comment added that submissions for zinc oxide as a skin protectant in concentrations up to and including 40 percent were made to the Advisory Review Panel on OTC Miscellaneous External Drug Products, which classified zinc oxide in Category I at these concentrations (Ref. 1).

The agency acknowledges that the Topical Analgesic Panel did not receive data demonstrating the safety and effectiveness of zinc oxide as a skin protectant in concentrations above 25 percent. The product cited by the comment was submitted to the Miscellaneous External Panel and contained 40 percent zinc oxide as an active ingredient for the treatment of diaper rash (Ref. 2). The Miscellaneous External Panel did not review and classify individual ingredients for use in treating diaper rash, but rather recommended inclusion of zinc oxide in the skin protectant rulemaking for diaper rash claims without discussing specific concentrations. That Panel's recommendations on diaper rash drug products were incorporated into this rulemaking on September 7, 1982 (47 FR 39436). The agency will address these recommendations in the **Federal Register** at a later date. At this time, the agency has made no decision on the upper limit concentration for zinc oxide in diaper rash products. Because no additional data were submitted on the use of these higher concentrations of zinc oxide for other skin protectant claims, the agency is not proposing to increase these limits as this time.

References

(1) Minutes of the Fourteenth Meeting of the Advisory Review Panel on OTC Miscellaneous External Drug Products, November 12 and 13, 1976.

(2) OTC Volume 160021.

17. One comment noted that the Panel presented a chart that clearly identifies which active ingredients can be used to treat the symptoms of "dryness," "wetness," or "friction (lubricity)" (43 FR 34632), but that this information is not stated in the monograph. The comment requested that the type of information that appears in the chart be incorporated into the monograph.

As stated in comment 22 below, the agency is proposing to revise the types of labeling claims recommended by the Panel, and the terms "dryness," "wetness," and "lubricity" will not be proposed in the tentative final monograph. The tentative final monograph specifically states which ingredients can bear the various labeling claims. A summary chart appears in comment 22 below.

C. Comments on Testing of Skin Protectant Drug Products

18. One comment recommended four changes in the Panel's suggested methods of testing to upgrade a wound-healing aid ingredient from Category III to Category I.

The agency has not addressed specific testing guidelines in this document. In revising the OTC drug review procedures relating to Category III, published in the **Federal Register** of September 29, 1981 (46 FR 47730), the agency advised that tentatively final and final monographs will not include recommended testing guidelines for conditions that industry wishes to upgrade the monograph status. Instead, the agency will meet with industry representatives at their request to discuss testing protocols. The revised procedures also state the time in which test data must be submitted for consideration in developimg ther final monograph. (See also part II. paragraph

A.2 below—*Testing of Category II and Category III conditions.)*

19. One comment pointed out an inconsistency in two Panel statements regarding Category III testing (43 FR 34647). The first statement would have allowed 2 years to develop the methodology for wound-healing studies in human subjects. The second statement recommended reclassifying the claim "aids wound healing" in Category II if adequate data to support it were not obtained in 2 years. The comment stated that it was not possible to develop methodology and perform investigations at the same time and that a 2-year time limit was not adequate.

Since the Panel's report was published in 1978, revisions in the procedural regulations for the OTC drug review have been made as a result of the Court ruling in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). The revised procedural regulations, published in the **Federal Register** of September 29, 1981 (46 FR 47730), provide that any testing necessary to resolve a Category III condition must be done before the publication of the relevant final monograph. In order to facilitate the development and submission of data to support changing a Category II or Category III classification, the agency has worked out procedures that were published in the same issue of the **Federal Register** as the revised regulations (46 FR 47740). These procedures cover review of proposed protocols by the agency and agency feedback on submitted data.

20. One comment contended that the Panel's requirement of three separate studies exceeds the "new drug" requirement of two adequate and well-controlled studies and is not necessary to confirm the extensive effectiveness data already submitted on live yeast cell derivative.

As discussed in comment 18 above, the agency will not address specific testing guidelines in this document. The number and extent of studies necessary to demonstrate effectiveness can only be resolved after the agency has met with industry representatives at their request to discuss testing protocols. For further information on testing protocols see comment 18 above and the agency's statement on testing Category II and Category III conditions in part II. paragraph A.2. below.

D. Comments on Labeling of Skin Protectant Drug Products

21. Two comments contended that FDA does not have the authority to legislate the exact wording of OTC labeling claims to the exclusion of what the comments described as other equally truthful claims for the products. The comments objected to the labeling recommended by the Panel as being overly restrictive and recommended that more flexibility in labeling be permitted by adding the following statement to each list of approved claims: "* * * or similar indication statements which are in keeping with the Panel's report."

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 monographs 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.

22. Several comments requested that the Panel's recommended indications in § 347.50(b)(7) (i) and (ii) be revised to make them more meaningful to consumers. Some comments stated that some of the indications were "cosmetic" in character, e.g., use of terms such as "soothes" or "gives comfort"; other comments questioned whether words such as "intertrigo" or "galling" would be understood by the ordinary consumer. One comment specifically objected to the use of the word "lubrication," stating that in general use the words "lubricate" and "lubricating" are understood to involve an oily or greasy substance used in machines to reduce friction and citing one dictionary definition to support this contention. The comment added that while some OTC skin protectant drug products, such as petrolatum, may be greasy, other product forms, such as powders, reduce friction without being greasy. The comment argued that consumers who do not want to use an oily or greasy substance may not use a product that is indicated for "lubrication" purposes; therefore, alternative words such as "soothing" or "smoothing" would better communicate to consumers the intended use of these products. One comment suggested that manufacturers be provided some flexibility in indications by arranging the Panel's recommended labeling into two groups and allowing manufacturers to label their products as they desire, especially if space limitations so require. The comment suggested that the indications be arranged as follows so that any phrase in column (1) may be combined with one or more terms in column (2):

(1)	(2)
Aids in temporary relief of	minor skin irritations
For the temporary protection	minor burns
Soothes	sunburn
Gives comfort to	windburn
For symptoms of chapping due to	scrapes
For symptoms of peeling due to	abrasions
For symptoms of scaling due to	cracked lips
For the lubrication of	
For symptoms of	intertrigo chafing galling rubbing friction

Another comment suggested that manufacturers be provided the option of describing the mode of action, e.g., absorbent, adsorbent, emollient, lubricant, in the labeling of the product.

The agency concurs that the Panel's recommended indications in § 347.50(b)(7) (i) and (ii) could be revised to make them more meaningful to consumers and to better reflect the "drug" use of these products. Many of the ingredients reviewed by the Panel have been used in both drug and cosmetic products for many years, and there has been an overlapping of

labeling claims. The agency has reviewed all of the labels for the marketed products submitted to the Panel and has reviewed all of the Panel's evaluations of these ingredients in an effort to identify historical drug claims for these ingredients. Most of the ingredients reviewed by the Panel are currently, or have been in the past, listed in the official drug compendia.

The agency has also reviewed all of the Category I labeling claims recommended by the Panel and determined that a number of these appear inappropriate for OTC drug labeling. Terms such as "intertrigo" and "galling" are not found in labeling for marketed OTC products submitted and reviewed by the Panel and would not be familiar to consumers; "contact dermatitis" is not readily self-diagnosable. The term "minor skin irritations" when used alone is too broad and would give consumers the impression that a skin protectant could or should be used for every type of minor skin irritation that occurs. The agency does not think that was the Panel's intent and points out that other types of skin remedies, e.g., external analgesic drug products, would be used to treat other types of skin irritations involving itching or pain. The agency considers the terms "soothes," "smoothing," "rubbing," "friction," and "lubrication" to be cosmetic claims in the context of skin protectant products. Symptoms of peeling or scaling may be interpreted differently by consumers, and the agency believes that stating that the product helps prevent or temporarily protects chafed and chapped skin or lips is more informative to the consumer. The term "abrasions," as recommended by the Panel, has not been included in the Category I labeling proposed for topical antibiotic and antimicrobial drug products. Instead, the term "scrapes" was used. Likewise, the agency believes that the term "scrapes" is more appropriate for skin protectant drug products.

The agency believes that the following labeling would adequately represent the drug uses of skin protectant drug products and is proposing the following in this tentative final monograph:

(1) "For the temporary protection of minor cuts, scrapes, burns, and sunburn."

(2) "Helps prevent and temporarily protects chafed, chapped, cracked, or windburned skin and lips."

(3) "Dries the oozing and weeping of poison ivy, poison oak, and poison sumac."

Based on the Panel's recommendations, the agency is proposing that the Category I ingedients included in the tentative final monograph be labeled with one or two of the three indications above as follows:

Ingredients	Indications		
	1	2	3
Allantoin	X	X	
Cocoa butter	X	X	
Petrolatum	X	X	
White petrolatum	X	X	
Shark liver oil	X	X	
Dimethicone		X	
Glycerin		X	
Aluminum hydroxide gel			X
Calamine			X
Corn starch[1]			X
Kaolin			X
Sodium bicarbonate[2]			X
Zinc acetate			X
Zinc carbonate			X
Zinc oxide			X

[1] Deferred until diaper rash drug products are reviewed.
[2] Deferred to External Analgesic Rulemaking (see comment 33 below).

The permitted combinations in § 347.20 have been clarified to reflect the labeling indications above.

Based on these indications, the agency sees no need for requiring a description of the mode of action (e.g., adsorbent, absorbent) in the labeling. The agency believes that such additional information would not necessarily increase the consumer's understanding of the use of these products.

The rulemaking for skin protectant drug products was reopened on September 7, 1982 (47 FR 39436) to include the Miscellaneous External Panel's recommendations for diaper rash, astringent, external fever blister, insect bite neutralizer, and poison ivy, oak, and sumac prevention drug products. It is possible that the indications for skin protectant drug products will be expanded in the future to include some of these other uses. For example, a number of the Category I ingredients are used in diaper rash drug products. Corn starch is one of these ingredients. At the present time, none of the proposed Category I indications are applicable to corn starch. Most of the uses of corn starch discussed by the Topical Analgesic Panel are cosmetic uses. The primary OTC drug use of corn starch appears to be in diaper rash drug products. Therefore, the agency is not including corn starch in the tentative final monograph until its use in diaper rash drug products is reviewed.

23. One comment questioned whether the Panel, in recommending general warnings for a class of ingredients, considered the applicability of each warning to each individual ingredient in the class. The comment acknowledged that the Panel's recommendations could always be altered by petitioning the agency for a change, but contended that there should be no need to go through the petitioning process to eliminate requirements that are clearly not applicable to a specific ingredient.

The agency believes that, in recommending general warnings for skin protectants as a class, the Panel considered the applicability of the warnings to specific ingredients in the class. For example, the Panel recommended specific warnings for seven different skin protectant ingredients in § 347.50(c) (4) through (10). The agency has revised these warnings in a few instances and is proposing to delete some of the general warnings from the labeling the Panel recommended for certain skin protectant drug products, e.g., lip balms. (See comments 26, 28, 29, and 31 below and part II. paragraph B.12. below.) Interested persons who disagree with the agency's proposal need not petition the agency at this time to request changes. Instead, they may submit written comments and objections following publication of this tentative final monograph. Finally, interested persons may petition the agency for a change following issuance of the final monograph. The agency expects that, throughout the skin protectant rulemaking process, labeling requirements for specific ingredients will continue to be identified and thoroughly evaluated so that the final monograph will contain appropriate warnings.

24. One comment wished to reserve the right to decide after issuance of the final skin protectant monograph whether it would be appropriate to petition the agency to exempt petrolatum from the two general warnings prescribed in 21 CFR 330.1(g) ("Keep this and all drugs out of the reach of children" and "In case of accidental ingestion, seek professional assistance or contact a Poison Control Center Immediately.")

The two general warnings in 21 CFR 330.1(g) are not required in the labeling of OTC skin protectant drug products until a final monograph becomes effective for those products. As stated in § 330.1(g), all interested parties have the opportunity to petition for exemption from these general warnings at any time.

25. One comment strongly urged that petrolatum be exempt from the Panel's recommended warning in § 347.50(c)(2): "Avoid contact with the eyes." The comment referred to studies that showed that ophthalmic ointments did not interfere with corneal wound-healing (Ref. 1) and cited the classification of petrolatum by the Advisory Review Panel on OTC

Ophthalmic Drug Products as a Category I active ingredient in ophthalmic preparations and the "Physician's Desk Reference" listing of white petrolatum as a vehicle for numerous ophthalmic preparations. The comment contended that products containing white petrolatum are routinely used to treat diseased eyes and that the warning to "avoid contact with the eyes" is therefore unnecessary for petrolatum. The agency disagrees. It is possible for petrolatum that is not prepared for ophthalmic use to be contaminated and cause infection if placed in or near the eyes. Ophthalmic ointments containing petrolatum are sterilized so as not to introduce a source of infection to the eye or cornea. Nonophthalmic products containing petrolatum for topical use are not sterilized and should not be used in the eyes. The agency is therefore proposing the Panel's recommended warning in the tentative final monograph.

Reference

(1) Hanna, C., et al., "The Effects of Ophthalmic Ointments on Corneal Wound Healing," *American Journal of Ophthalmology*, 75:193–200, 1973.

26. One comment suggested that the Panel's recommended warning statement in § 347.50(c)(3), which reads "Discontinue use if symptoms persist for more than 7 days and consult a physician," be revised to read "If condition does not improve within 7 days, discontinue use and see your doctor." The comment contended that the Panel's recommended warning could be misinterpreted by some consumers and could result in unnecessary visits to the doctor, whereas the revised warning recognizes that the condition being treated may "improve" but still "persist." The comment stated that if the condition improves, it is unnecessary to encourage the consumer to visit a doctor. Another comment stated that the warning was not justified for petrolatum, adding that a brief delay in seeking medical attention would not create a hazard. The comment argued that if the consumer is going to heed the warning, then both "discontinue use" and "consult a physician" are not necessary, and referring the consumer to a physician should take precedence over telling the consumer to stop use of the drug. The comment suggested that the warning for petrolatum be shortened to "If symptoms persist, consult a physician," or "If symptoms persist, see your doctor."

The agency believes consumers should be advised that if the condition gets worse or does not improve after 7 days, a doctor should be consulted. The agency agrees that referring the consumer to a doctor is more important than telling the consumer to stop use of the drug. Therefore, the agency is proposing that the warning in § 347.50(c)(3) be revised to read: "If condition worsens or does not improve within 7 days, consult a doctor," While the consumer may continue to use the skin protectant product, the purpose of the warning is to convey to the consumer the message to seek medical care if improvement does not occur.

27. One comment contended that petrolatum is an excellent example of an ingredient generally recognized as safe; therefore, it seems somewhat contradictory that so many warnings (a total of six to date) have already been proposed for this ingredient, when several other panels that are also reviewing petrolatum have yet to be heard from.

The agency concurs that petrolatum is safe when used properly; however, some warnings are necessary to prevent improper use. The warning recommended by the Panel in § 347.50(c)(1) is a general warning for all externally applied products. The warnings proposed in § 347.50(c) (2) and (3) are discussed in comments 25 and 26 above. The warning recommended by the Panel in § 347.50(c)(7) is important to prevent improper use of petrolatum on puncture wounds, infections, and lacerations. (See part II. paragraph B.12. below.) The two general warnings required by § 330.1(g) are discussed in comment 24 above. The agency believes that the proposed warnings for petrolatum used as a skin protectant are necessary. Other panels that have evaluated petrolatum for other uses have recommended warnings related to those uses. The agency will review the recommended warnings for petrolatum in the various rulemakings and will propose appropriate warnings as necessary.

28. Several comments urged that the warning "For external use only" not be required for lip balm products. One comment claimed that 21 CFR 82.3(n) defines externally applied drugs as those "which are applied * * * not to the lips * * *," thus concluding the warning to be contradictory and confusing to the consumer. The comment also contended that consumers would not confuse a solid stick dosage form with a liquid medication that could be swallowed. Another comment believed that the warning, when read in context with the poison control warning required by 21 CFR 330.1(g), implies danger in using lip balms, thus discouraging use and increasing the incidence of chapping, cracking, and irritation of the lips. A third comment objected to the warning specifically for petrolatum-containing lip blam products. The comment contended that any hazard from the accidental ingestion of petrolatum is nonexistent, adding that the Panel stated that large amounts of petrolatum are essentially nontoxic when ingested (43 FR 34639); that petrolatum is regulated as an approved food additive by FDA in accordance with 21 CFR 172.880 and the Food Chemicals Codex; that with 424 million units distributed, only 10 adverse incidents have been reported, and these were not related to ingestion; and that the Advisory Review Panel on OTC Hemorrhoidal Drug Products found petrolatum safe and effective for intrarectal use.

The agency agrees with the comments. Although 21 CFR 82.3(n) is not applicable to drug active ingredients but to certified colors, the agency believes that lip balm products do not require the warning "For external use only" to assure safe use. Therefore, the agency is proposing that the warning in § 347.50(c)(1) is not required for lip balm products. (See comment 31 below.)

29. One comment urged that the Panel's recommended warning in § 347.50(c)(2), "Avoid contact with the eyes," should not be required for lip balms because the products' solid form will not run into the eyes and cannot be accidentlly splashed or poured into the eyes. The company submitting the comment added that it had sold millions of tubes of lip balm over 20 years and was not aware of a single complaint of irritation of the eyes.

The agency concurs with the comment that lip balms would not normally be used in or near the eyes and is proposing that the above warning not be required for lip balm products.

30. Two comments requested deletion for lip balms of the warning in § 347.50(c)(3), "Discontinue use if symptoms persist for more than 7 days and consult a physician." One comment contended that lip balms help protect against and heal chapped and dried lips and are not for treatment of a disease state, that the warning may discourage consumer use of these products, that discontinuing use increases the likelihood of symptoms occuring, that the 7-day time limitation imparts a sense of danger to the consumer, and that the warning is inconsistent with the directions for a lip balm, "Apply liberally as oftern as necessary." The second comment contended that the warning should be limited to products with indications for conditions such as

scrapes, burns, or weeping. The comment maintained that the warning should not apply to lip balms intended for chapped lips and the soothing of dry lips which could persist for many days under harsh climatic conditions.

The agency is proposing to revise the warning in § 347.50(c)(3) to read "If condition worsens or does not improve within 7 days, consult a doctor." (See comment 26 above.) The agency believes that this warning is needed for lip balms to alert consumers to consult a doctor if the condition does not improve after 7 days. Chapped lips can be caused by diseases which, if undiagnosed and untreated, can be harmful, e.g., cheilosis, a disease condition associated with deficiency of some B vitamins and characterized by fissuring and dry scaling of the surface of the lips (Ref. 1). The agency has modified the warning to refer to conditions rather than symptoms and believes that the revised warning is not inconsistent with the directions, "Apply liberally as often as necessary."

Reference

(1) Berkow R., editor, "The Merck Manual," 13th Ed., Merck and Co., Rahway, NJ, p. 1671, 1977.

31. Two comments requested that petrolatum-containing lip balms be exempt from the warning, "Not to be applied over puncture wounds, infections, or lacerations" recommended by the Panel in § 347.50(c)(7). One comment contended that the warning is appropriate for petrolatum marketed as a first-aid ointment, but is inappropriate for lip balms in which the petrolatum is combined with waxes to form a solid stick for use on chapped lips. The second comment asked that dimethicone-containing lip balms also be exempt from the same warning appearing in § 347.50(c)(5) for dimethicon, contending that lip balms containing dimethicone or petrolatum would not be mistakenly used on the conditions listed in the warning.

The agency agrees with the comments and believes that consumers would not mistakely use lip balms to treat puncture wounds, infections, or lacerations. Accordingly, the agency is proposing in the tentative final monograph that this warning not be required for lip balm products. The agency will further consider the "infection" part of this warning for the use of petrolatum-containing lip balms in the future when it evaluates the Miscellaneous External Panel's Statement on Drug Products for the Treatment of Fever Blisters, which will be incorporated into this rulemaking proceeding. Therefore, at this time, the agency is proposing the following statement in § 347.50(c) of the tentative final monograph:

"(9) *For products formulated as lip balms.* The warnings in paragraph (c) (1), (2), and (4) of this section are not required for lip balm products." (See comments 28 and 29 above.)

32. Several comments noted that it may not be possible to put all the required labeling recommended in § 347.50 on small containers without using cartons or package inserts. The comments urged that flexibility in wording be allowed on these small containers. One comment pointed out the petrolatum is a multipurpose active ingredient which was reviewed by several panels; that, because of its multipurpose character, labeling requirements may become cumbersome and confusing to consumers; and that it would be impossible to place several panels' different indications, warnings, and directions for the different uses of the product on small containers. The second comment suggested combining the indication allowed in § 347.50(b)(5), "For symptoms of chapping, peeling or scaling due to sunburn, windburn, or cracked lips," with the directions in § 347.50(d), "Apply liberally as often as necessary," to read "Apply liberally as needed for dry, chapped lips, wind or sunburned lips," adding that this shorter version would convey the same message. A third comment recommended that lip balm drug products be exempt from the warnings proposed in § 347.50(c) (1), (3), (5), and (7). The comment contended that the warnings are unnecessary, of no benefit to the public, and cannot be labeled conspicuously on small packages, as section 502(c) of the act would require. The comment also contended that off-package labeling would increase production costs and waste natural resources.

The agency has reviewed the Panel's recommended labeling and, wherever possible, has revesed the labeling so that only essential information is required. (See comments 22, 25, 26, and 27 above.) The agency has also deleted a number of warnings for products formulated as lip balms, including some the comment requested be deleted. (See comments 28, 29, and 31 above.) The agency believes that the labeling proposed in this tentative final monograph is necessary to assure proper and safe use of OTC drugs by the public and will not be confusing to consumers. Accordingly, the agency recommends that when an OTC skin protectant drug product is packaged in a container that is too small to contain the required labeling, the product be enclosed in a carton or be accompanied by a package insert that complies with the monograph.

33. On comment requested that sodium bicarbonate (baking soda) be exempted from the recommended warnings in § 347.50(c) (1), (2), and (9). Section 347.50(c)(1) states "For external use only." The comment contended that because sodium bicarbonate is both a food and an antacid, this warning statement would confuse the consumer. Section 347.50(c)(2) states "Avoid contact with the eyes." The comment contended that sodium bicarbonate is nonirritating according to the Draize Rabbit Eye Irritation Test and it is used in swimming pools and baths. Section 347.50(c)(9) states "Do not apply to extensive acid burns. Flood acid burns with cold tap water and consult a physician." The comment stated this warning should only be required when the label bears indications for relief from minor burns and sunburns.

In its evaluation of sodium bicarbonate, the Panel pointed out that sodium bicarbonate is an effective antipruritic in relieving itching due to nonpoisonous insect stings and bites or due to sunburn. It is also used to relieve the pain of minor acid burns (43 FR 34640). Because the indication "for the temporary relief of pain and itching due to minor burns, sunburn, * * *, insects bites, and minor skin irritations" is being specifically addressed in the rulemaking for OTC external analgesic drug products (44 FR 69768), the agency is transferring sodium bicarbonate to that rulemaking proceeding. The Topical Analgesic Panal also recommended that products containing any external analgesic active ingredient bear the warnings "For external use only" and "Avoid contact with the eyes." The agency will address the comment's statements about the applicability of these warnings to products containing sodium bicarbonate prior to the publication of a final monograph for external analgesic drug products in a future issue of the **Federal Register.** The Panel's recommended warning is § 347.50(c)(9) relating to acid burns will also be discussed in that publication.

34. One comment suggested substituting the term "concentration" for "dosage" in §§ 347.10 and 347.20. The comment explained that the term "dosage" is not accurate when read in context with the directions for use in §347.50(d).

The agency agrees with the comment. Accordingly, "dosage" has been changed to "concentration" where applicable in the tentative final monograph.

35. One comment requested that manufacturers not be required to put "directions for use" on petrolatum labels or at least have this option when label space limitations are a problem. This request was based on 21 CFR 201.116, which provides that the requirement for placing directions for use on labels can be omitted "insofar as adequate directions for common uses thereof are known to the ordinary individual." The comment concluded that petrolatum's long history of use qualifies it for this exemption.

Because petrolatum is used for many different indications, the agency believes that not including directions for use in the labeling might confuse consumers. It is also possible that consumers might not use the product as often as needed. Therefore, in the consumer's best interest, the agency is proposing that "directions" be required for petrolatum.

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 claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and is proposing the following categorization of skin protectant active ingredients. For the convenience of the reader, the following table is included as a summary of the categoriation of skin protectant active ingredients by the Panel and the proposed classification by the agency:

Skin protectant active ingredients	Panel	Agency
Allantoin[1]	I	I.
Aluminum hydroxide gel	I	I.
Bismuth subnitrate	II	II.
Boric acid	II	II.
Calamine	I	I.
Cocoa butter	I	I.
Corn starch	I	([3])
Dimethicone	I	I.
Glycerin	I	I.
Kaoline	I	I.
Live yeast cell derivative[2]	III	III.
Petrolatum	I	I.
Shark liver oil	I	I.
Sodium bicarbonate	I	([4])
Sulfur	II	II.
Tannic acid	II	II.
White petrolatum	I	I.
Zinc acetate[1]	I	I.
Zinc carbonate	I	I.
Zinc oxide	I	I.

[1]Also classified by the Panel and the Agency as a Category III wound. healing agent.
[2]Classified only as a wound healing agent.
[3]Deferred.
[4]Transferred.

2. *Testing of Category II and Category III conditions.* The Panel recommended testing guidelines for skin protectant drug products (43 FR 34647). The agency is offering these guidelines as the Panel's recommendations without adopting them or making any formal comment on them. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any skin protectant ingredient or 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 has added the word "drug" to the *"Scope"* in § 347.1 of the tentative final monograph and to the definition of skin protectant in § 347.3 to emphasize that the monograph covers only drug products and does not cover cosmetic products. (See comment 6 above.)

2. The agency has revised the definition of a skin protectant drug. (See comment 7 above.)

3. The agency is redesignating proposed Subpart D as Subpart C and placing the labeling sections of the monograph under Subpart C.

4. The agency is deferring review of the Panel's recommended warning limiting the use of shark liver oil and liver yeast cell derivative on children under 2 years of age until it reviews the use of these ingredients as part of its evaluation of diaper rash drug products. (See comment 12 above.)

5. The agency is not including corn starch in the monograph until diaper rash drug products are reviewed. (See comment 22 above.)

6. The agency has revised the labeling indications recommended by the Panel, and the permitted combinations in § 347.20 have been clarified to reflect the revised labeling indications. (See comment 22 above.)

7. The agency has revised the Panel's recommended warning statement in § 347.50(c)(3). (See comment 26 above.)

8. The agency has exempted lip balm drug products from the warnings in § 347.50(c) (1), (2), and (4). (See comments 28, 29, and 31 above.) To clarify the meaning of "lip balm," the agency is adding a definition of this term to § 347.3.

9. The agency has transferred sodium bicarbonate to the rulemaking for OTC external analgesic drug products. (See comment 33 above.)

10. The agency has substituted the term "concentration" for "dosage" where appropriate in the tentative final monograph. (See comment 34 above.)

11. 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.

12. The Panel proposed the same warning for dimethicone in § 347.50(c)(5) and for petrolatum and white petrolatum in § 347.50(c)(7). The agency proposes to redesignate this warning as § 347.50(c)(4) and to make it applicable to all skin protectants labeled with the same indications as dimethicone, petrolatum, or white petrolatum. The agency further proposes to revise this warning to include the term "deep" to describe wounds that should not be self-treated with these skin protectants and to advise consumers to consult a doctor for such wounds. These revisions are proposed because deep wounds, as well as puncture wounds, should be treated by a doctor for adequate protection against tetanus. As revised, the proposed warning for products labeled according to § 347.50(b) (1) or (2) reads as follows: "Not to be applied over deep or puncture wounds, infections, or lacerations. Consult a doctor."

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 skin protectant products may have to be reformulated to delete

nonmonogrpah 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 skin protectant 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 skin protectant 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 skin protectant 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 determined that under 21 CFR 25.24(d)(9) (proposed in the **Federal Register** of December 11, 1979; 44 FR 71742) this proposal is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects in 21 CFR Part 347

OTC drugs, Skin protectants.

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 347 to read as follows:

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

Subpart A—General Provisions

Subpart B—Active Ingredients

Subpart C—Labeling

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

Subpart A—General Provisions

§ 347.1 Scope.

(a) An over-the-counter skin protectant drug product in a form suitable for topical administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this part and each of the general conditions 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.

§ 347.3 Definitions.

As used in this part:

(a) *Skin protectant.* A drug which protects injured or exposed skin or mucous membrane surface from harmful or annoying stimuli.

(b) *Lip balm.* A drug product that relieves and prevents dryness or chapping of the exposed surface of the lips.

Subpart B—Active Ingredients.

§ 347.10 Skin protectant active ingredients.

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

(a) Allantoin, 0.5 to 2 percent.

(b) Aluminum hydroxide gel, 0.15 to 5 percent.

(c) Calamine, 1 to 25 percent.

(d) Cocoa butter, 50 to 100 percent.

(e) Dimethicone, 1 to 30 percent.

(f) Glycerin, 20 to 45 percent.

(g) Kaolin, 4 to 20 percent.

(h) Petrolatum, 30 to 100 percent.

(i) Shark liver oil, 3 percent.

(j) White petrolatum, 30 to 100 percent.

(k) Zinc acetate, 0.1 to 2 percent.

(l) Zinc Carbonate, 0.2 to 2 percent.

(m) Zinc oxide, 1 to 25 percent.

§ 347.20 Permitted combinations of active ingredients.

(a) Any two or more of the ingredients identified in § 347.10 (a), (d), (h), (i), and (j) may be combined provided the combination is labeled according to § 347.50(b)(1) and provided each ingredient in the combination is within the concentration specified in § 347.10.

(b) Any two or more of the ingredients identified in § 347.10 (a), (d), (e), (f), (h), (i), and (j) may be combined provided the combination is labeled according to § 347.50(b)(2) and provided each ingredient in the combination is within the concentration specified in § 347.10.

(c) Any two or more of the ingredients identified in § 347.10 (b), (c), (g), (k), (l), and (m) may be combined provided the combination is labeled according to § 347.50(b)(3) and provided each ingredient in the combination is within the concentration specified in § 347.10.

Subpart C—Labeling

§ 347.50 Labeling of skin protectant 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 a "skin protectant."

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

(1) *For products containing any ingredient in § 347.10 (a), (d), (h), (i), and (j).* "For the temporary protection of minor cuts, scrapes, burns, and sunburn."

(2) *For products containing any ingredient in § 347.10 (a), (d),. (e), (f), (h), (i), and (j).* "Helps prevent and temporarily protects chafed, chapped, cracked, or windburned skin and lips."

(3) *For products containing any ingredient in § 347.10 (b), (c), (g), (k), (l), and (m).* "Dries the oozing and weeping of poison ivy, poison oak, and poison sumac."

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

(1) "For external use only."

(2) "Avoid contact with the eyes."

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

(4) *For products labeled according to § 347.50(b) (1) or (2).* "Not to be applied over deep or puncture wounds, infections, or lacerations. Consult a doctor."

(5) *For products formulated as lip balms.* The warnings in paragraph (c) (1), (2), and (4) of this section are not required for lip balm products.

(6) *For products containing aluminum hydroxide gel identified in § 347.10(b).* "Do not use on children under 6 months of age without consulting a doctor."

(7) *For products containing glycerin identified in § 347.10(f).* "Do not use on children under 6 months of age without consulting a doctor."

(8) *For products containing zinc acetate identified in § 347.10(k).* "Do not use on children under 2 years of age without consulting a doctor."

(d) *Directions.* The labeling of the product contains the following statement under the heading "Directions": "Apply liberally as often as necessary."

(e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements above.

Interested persons may, on or before April 18, 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 15, 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 office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register.**

Interested persons, on or before February 15, 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 16, 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 office above 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 16, 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 27, 1983.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Richard S. Schweiker,

Secretary of Health and Human Services.

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