

any rulemaking in the OTC drug review, concluded that additional data are needed, and placed these ingredients in Category III.

Because no data were submitted to support the effectiveness of vitamins A and D for skin protectant uses, the agency concludes that these ingredients are nonmonograph when used individually or in combination other than as a component of cod liver oil listed in § 347.10(e) of this final monograph.

(Comment 34) In the TFM for OTC first aid antiseptic drug products (56 FR 33644 at 33650), the agency deferred data on a physical barrier cream product with protective claims to the rulemaking for OTC skin protectant drug products. The cream product contains a combination of ingredients: Cetyl alcohol, glyceryl stearate, isopropyl palmitate, stearyl alcohol, and beeswax, labeled as "skin wound protectant" ingredients. The product labeling states "helps protect minor cuts, burns, and skin irritations against contamination." This claim is very similar to the claim included in § 347.50(b)(1) of this final monograph. The submission included the results of animal and human safety studies on the finished product, including LD50 in mice and rats, acute dermal toxicity studies in rabbits, 48-hour and 72-hour primary irritation studies in humans using occlusive patch tests, and 21-day cumulative irritation studies. The submission also included reports of studies on the cream product's protective barrier effect and a clinical study to evaluate safety and effectiveness. The clinical study was described as a randomized, controlled, double-blind, parallel-group comparison of two products to determine the cream product's safety and effectiveness under actual use conditions. The control formulation was not provided.

The agency finds the submitted data insufficient to establish the skin protectant effect of any of the ingredients present in the cream product because the contribution, if any, of each of the individual active ingredients cannot be determined. The Panel recommended that there need be no limit to the number of skin protectant ingredients that may be combined in a product (43 FR 34628 at 34631). However, each ingredient must make a contribution to the claimed effect(s) in order to be deemed an active ingredient (§ 330.10(a)(4)(iv)). Further, the agency notes that the Miscellaneous External Panel classified the ingredients cetyl alcohol and stearyl alcohol as inactive in the advance notice of proposed rulemaking for OTC alcohol drug products (47 FR 22324 at 22326,

May 21, 1982). In addition, the Dental Panel classified beeswax as inactive in the advance notice of proposed rulemaking for OTC drug products for the relief of oral discomfort (47 FR 22712 at 22715). No additional data on these three ingredients have been submitted to any rulemaking in the OTC drug review. The other two listed active ingredients, glyceryl stearate and isopropyl palmitate, have not been considered in any rulemaking in the OTC drug review. Consequently, the agency concludes that the safety and effectiveness data are insufficient on beeswax, cetyl alcohol, glyceryl stearate, isopropyl palmitate, and stearyl alcohol. Therefore, these ingredients are being included in § 310.545(a)(18) as nonmonograph.

(Comment 35) Two comments contended that, as a class, skin protectant ingredients may be combined with more different types of therapeutic categories than any other class of ingredients. However, in the TFM, proposed § 347.20 does not list any ingredients other than skin protectant ingredients that may be combined. The comments stated that skin protectant ingredients have been found appropriate for use in combination with several other ingredient categories in other OTC drug product rulemakings. The comments requested that the agency include a provision in the final monograph allowing the combination of skin protectant ingredients with any therapeutic class of ingredients when such a combination has been found appropriate by any other OTC advisory review panel.

Proposed § 347.20 in the skin protectant TFM was published in the **Federal Register** on February 15, 1983, before the TFMs for many other categories of OTC drug products. Subsequently, based on panel recommendations in other OTC drug rulemakings and the TFMs for OTC external analgesic drug products (48 FR 5852 at 5868), OTC first aid antiseptic drug products (56 FR 33644 at 33677), and OTC sunscreen drug products (58 FR 28194 at 28296, May 12, 1993), this final monograph includes skin protectant active ingredients in combination with other ingredients from these therapeutic classes.

Therefore, the agency has further considered and expanded the ingredient combinations included in § 347.20 of this final monograph, including skin protectant-sunscreen combinations in § 347.20(d). The agency is also amending the final monograph for OTC sunscreen drug products (64 FR 27666, May 21, 1999) to include sunscreen-skin protectant drug products. Further, the

agency may be expanding the permitted combinations in § 347.20(b) and (c) as data submitted to the rulemakings for OTC external analgesic and first aid antiseptic drug products are evaluated and the final monographs for those OTC drug classes are issued.

### III. Conclusion

Based on the available evidence, the agency is issuing a final monograph establishing conditions under which OTC skin protectant drug products are generally recognized as safe and effective and not misbranded. Any drug product labeled, represented, or promoted for use as an OTC skin protectant drug that contains any of the ingredients listed in § 310.545(a)(18)(i)(A) or (a)(18)(i)(B) or that is not in conformance with the monograph (part 347) may be considered a new drug within the meaning of section 201(p) of the act (21 U.S.C. 321(p)) and misbranded under section 502 of the act. Such a drug product cannot be marketed for skin protectant uses unless it is the subject of an approved application under section 505 of the act (21 U.S.C. 355) and part 314 of the regulations (21 CFR part 314). An appropriate citizen petition to amend the monograph may also be submitted in accord with 21 CFR 10.30 and 330.10(a)(12)(i). Any OTC skin protectant drug product initially introduced or initially delivered for introduction into interstate commerce after the compliance dates of the final rule for § 310.545(a)(18)(i)(A) or this final rule that is not in compliance with the regulations is subject to regulatory action.

Our decision to revise the warnings set forth in this final rule is based on comments made in response to the proposed rule. Mandating warnings in an OTC drug monograph does not require a finding that any or all of the OTC drug products covered by the monograph actually caused an adverse event, and FDA does not so find. Nor does FDA's requirement of warnings repudiate the prior OTC drug monographs and monograph rulemakings under which the affected drug products have been lawfully marketed. Rather, as a consumer protection agency, FDA has determined that warnings are necessary to ensure that these OTC drug products continue to be safe and effective for their labeled indications under ordinary conditions of use as those terms are defined in the act. This judgment balances the benefits of these drug products against their potential risks (*see* 21 CFR 330.10(a)).