DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 347

[Docket No. 78N-021D]

RIN 0905-AA06

Skin Protectant Drug Products for Over-the-Counter Human Use; Proposed Rulemaking for Diaper Rash Drug Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking amending the tentative final monograph (proposed rule) for over-the-counter (OTC) skin protectant drug products. The proposed rulemaking would establish conditions under which OTC skin protectant drug products for the treatment or prevention of diaper rash are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the statement on OTC drug products for the treatment of diaper rash of the Advisory Review Panel on OTC Miscellaneous External Drug Products, public comments on an advance notice of proposed rulemaking that was based on that statement, and public comments on the notice of proposed rulemaking for OTC skin protectant drug products. (See the Federal Register of February 15, 1983; 48 FR 6820.) The agency's proposals concerning the use of other OTC diaper rash drug products are being published elsewhere in this issue of the Federal Register. These proposals are part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed rulemaking before the Commissioner of Food and Drugs by December 17, 1990. The agency is allowing a period of 180 days for comments and objections instead of the normal 60 days for the following reasons: (1) The concurrent publication of four rulemakings regarding OTC diaper rash drug products and (2) this document contains the agency's initial evaluation of the submissions of data on OTC diaper rash drug products that were made to, but not reviewed by, the Advisory Review Panel on OTC Miscellaneous External Drug Products (Miscellaneous External Panel). New data by June 20, 1991. Comments on the new data by August 20, 1991. Written comments on the agency's economic impact determination by December 17, 1990.

ADDRESSES: Written comments, objections, new data, 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.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION: In the Federal Register of September 7, 1982, FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), advance notices of proposed rulemaking and reopened the administrative records for OTC topical antifungal drug products (47 FR 39464), topical antimicrobial drug products (47 FR 39406), external analgesic drug products (47 FR 39412), and skin protectant drug products (47 FR 39436) to allow for consideration of a statement on OTC drug products for the treatment of diaper rash prepared by the Miscellaneous External Panel, which was the advisory review panel responsible for evaluating data on the active ingredients used for the treatment of diaper rash. Interested persons were invited to submit comments by December 6, 1982. Reply comments in response to comments filed in the initial comment period could be submitted by January 5, 1983.

In the Federal Register of December 28, 1982 (47 FR 57738), in response to a request for an extension of time, the comment period and reply comment period for OTC skin protectant drug products were extended to February 4, 1983, and to March 7, 1983, respectively.

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

Five drug manufacturers, one trade association, and one manufacturer of diapers submitted comments. Most of these comments are general in scope and were submitted to more than one of the four rulemakings mentioned above. In those cases where the same comments were submitted to more than one rulemaking, the comments are being addressed only once—in this notice of proposed rulemaking to amend the notice of proposed rulemaking for OTC skin protectant drug products. Copies of the comments received are on public display in the Dockets Management Branch.

The Panel provided a general statement on OTC drug products for the treatment of diaper rash, but did not review individual ingredients nor develop labeling for diaper rash drug products. The agency is aware that a number of diaper rash drug products are labeled for both the treatment and prevention of diaper rash. Therefore, the agency is expanding the scope of this rulemaking to include drug products labeled for both or either use.

In the Federal Register of February 15, 1983 (48 FR 6820), the agency published a tentative final monograph (proposed rule) for OTC skin protectant drug products. The agency issued this notice after considering the report and recommendations of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products (Topical Analgesic Panel) and public comments on an advance notice of proposed rulemaking that was based on those recommendations.

Interested persons were invited to submit comments by April 18, 1983, new data by February 15, 1984, and comments on the new data by April 16, 1984. In response to that notice, four drug manufacturers submitted comments concerning the use of skin protectant ingredients for diaper rash. The agency is also addressing these comments in this notice of proposed rulemaking. Copies of the comments received are on public display in the Dockets Management Branch (address above).

In this notice of proposed rulemaking, FDA responds to public comment and states for the first time its position on OTC skin protectant drug products for the treatment or prevention of diaper rash. Final agency action on this matter will occur with the publication at a future date of a final rule relating to OTC skin protectant drug products for use in diaper rash. Other documents concerning the use of OTC topical antifungal drug products, OTC topical antimicrobial drug products, and OTC external analgesic drug products for the treatment or prevention of diaper rash are being published separately, elsewhere in this issue of the Federal Register. This proposal constitutes FDA's tentative adoption of the Panel's statement on OTC skin protectant drug products for use in diaper rash as modified on the basis of the comments received and the agency's independent evaluation of the Panel's statement.

The OTC drug procedural regulations (21 CFR 330.10) now provide that any

testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA will no longer use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but will use instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the **Federal Register**. On or after that date, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. Further, any OTC drug product subject to this monograph that is repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

If the agency determines that any labeling for a condition included in the final monograph should be implemented sooner than the 12-month effective date, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notices published in the **Federal Register** of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179) or to additional information that has come to the agency's attention since publication of the advance notices of proposed rulemaking. The volumes are on public display in the Dockets Management Branch (address above).

I. The Agency's Tentative Conclusions on the Comments

The agency has reviewed the comments submitted to this rulemaking and, as noted above, determined that most of the comments were submitted to more than one of the four rulemakings related to OTC diaper rash drug products. The majority of the comments are general in scope or deal primarily with the use of skin protectant active ingredients. The agency has decided to address all of these general comments in a single rulemaking, which is this notice of proposed rulemaking to amend the tentative final monograph for OTC skin protectant drug products. Accordingly, the general comments regarding diaper rash as well as the portions of the comments that concerned skin protectant active ingredients are addressed below. The general comments applicable to the other three affected rulemakings are incorporated into those rulemakings, respectively.

A. General Comments

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

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products, published in the **Federal Register** of May 11, 1972 (37 FR 9464), and in paragraph 3 of the preamble to the tentative final monograph for antacid drug products, published in the **Federal Register** of November 12, 1973 (38 FR 31260). FDA reaffirms the conclusions stated in those documents. 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 that a separate and distinct rulemaking be established to encompass consideration of the safety and efficacy of OTC drug products for the treatment and prevention of diaper rash. The comments contended that diaper rash drug products represent a well-established, separate, and distinctive product category and, thus, should be the subject of a separate OTC drug monograph. As an alternative to a separate monograph, one of the comments suggested that diaper rash drug products could be a clearly identifiable subsection of the monograph for OTC skin protectant drug products because diaper rash drug products, almost without exception, contain at least one skin protectant ingredient, or a combination of skin protectant ingredients, and many of these ingredients are already included in the rulemaking for OTC skin protectant drug products. This comment added that diaper rash products are considered as a separate product category in the *Handbook of Nonprescription Drugs* (Ref. 1).

The agency agrees that drug products for the treatment and prevention of diaper rash would be suitable for a separate and distinct rulemaking, but believes, as suggested by one of the comments, that these products could be included as a clearly identifiable subsection of the monograph for OTC skin protectant drug products. Because most of the ingredients used to treat and prevent diaper rash are also used as skin protectants, the agency concludes that incorporating the diaper rash ingredients and claims as a subpart of the skin protectant monograph will eliminate unnecessary duplication and make it easier for interested parties to locate the regulatory information related to these products. Likewise, any external analgesic, antimicrobial, or antifungal active ingredients that are Category I for diaper rash can be included in an appropriate subpart of their respective monographs.

Reference

(1) Smith, G.H., "Diaper Rash and Prickly Heat Products," *in* "Handbook of Nonprescription Drugs," 7th Ed., American Pharmaceutical Association, Washington, pp. 605–614, 1982.

3. Referring to the Panel's general discussion on diaper rash (47 FR 39406 at 39409, 39412 at 39416, 39436 at 39440, and 39464 at 39467), one comment requested removal of some of the Panel's statements regarding disposable diapers with a plastic backing. Contending that the Panel's remarks were anecdotal or superfluous and not supported by scientific data, the comment stated that these remarks were inappropriate for inclusion in an OTC drug monograph unless substantiated by

data acceptable to the scientific community.

The OTC drug review procedures do not preclude a panel from expressing its opinion about factors that may be related to the use of drug products being evaluated. In this instance, the Panel discussed disposable diapers with a plastic backing in relation to occlusion as a factor that may affect diaper rash. However, the Panel did not propose any labeling regarding the use of disposable diapers with a plastic backing.

Other panels have also discussed occlusion in relation to drug products that they reviewed. For example, the Topical Analgesic Panel discussed occlusion in relation to children under 2 years of age in its report on OTC external analgesic drug products stating, "Ingredients under occlusion may possibly be corrosive to the infant's skin," (44 FR 69768 at 69774). In its report on topical antifungal drug products, the Advisory Review Panel on OTC Antimicrobial (II) Drug Products (Antimicrobial II Panel) referred to "occlusive socks and stockings that increase sweating and favor the development of athletes foot," (47 FR 12480 at 12489). Disposable diapers are consumer products, not drugs, and therefore are not covered by OTC drug rulemaking proceedings. Consequently, the agency does not believe that there is a need to remove the requested statements from the Panel's discussion. Further, there is no need for any person to submit additional data or comments regarding disposable diapers with a plastic backing because such articles are outside the scope of this rulemaking and will not be further addressed in the tentative final monographs for OTC diaper rash drug products.

B. Comments on Labeling

4. Two comments contended that FDA cannot legally, and should not as a matter of policy, prescribe exclusive lists of terms for the indications for use for OTC drug products, thus prohibiting alternative OTC labeling terminology which is truthful, not misleading, and intelligible to the consumer. One comment added that its views on this subject were presented to FDA in connection with the September 29, 1982 hearing on the "exclusivity" policy.

After considering the testimony presented at the hearing held on September 29, 1982 and the written comments submitted to the record, FDA proposed in the **Federal Register** of April 22, 1985 (50 FR 15810) to change its exclusivity policy for the labeling of OTC drug products. In the **Federal Register** of May 1, 1986 (51 FR 16258), the agency published a final rule changing its labeling policy for stating the indications for use of OTC drug products. Under 21 CFR 330.1(c)(2), the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either (1) the specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "APPROVED USES"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "APPROVED USES"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "APPROVED USES", plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All other OTC drug labeling required by a monograph or other regulation (*e.g.*, statement of identity, warnings, and directions) must appear in the specific wording established under the OTC drug monograph or other regulation where exact language has been established and identified by quotation marks, *e.g.*, 21 CFR 201.63 or 330.1(g). The proposed rule in this document is subject to the labeling provisions in § 330.1(c)(2).

5. Three comments requested the following indications as Category I labeling for products used for the treatment of diaper rash: "Promotes healing," "protects skin," "relieves chafing," "effective in sealing out wetness and germs," "promotes healing, protects and helps seal out wetness," "aids in the (temporary) relief of minor skin irritations due to (associated with) diaper rash," "for the (temporary) protection of minor skin irritations due to (associated with) diaper rash," "soothes minor skin irritations due to (associated with) diaper rash," "gives comfort to minor skin irritation(s) due to diaper rash," and "for symptoms of chafing, rubbing, and inflammation of infant's skin due to diaper rash." One comment requested that prevention of diaper rash be included as part of the Category I labeling indications for skin protectants, while the other comments suggested the following indications for products used for the prevention of diaper rash: "Aids (helps) in the prevention of diaper rash."

The agency has evaluated the comments' requests and determined that a general statement that informs consumers what these products do would be an appropriate indications statement. Accordingly, the agency is proposing in § 347.50(b)(5) the following statement for products containing a suitable skin protectant active ingredient: "Helps treat and prevent diaper rash." The agency believes that it would also be helpful to describe for consumers the protectant action of these ingredients in treating diaper rash. Therefore, the agency is also including the following information as part of the indications proposed in 347.50(b)(5) for these products in this tentative final monograph: "Protects" (select one of the following: "chafed skin" or "minor skin irritation") (select one of the following: "due to" or "associated with") "diaper rash and helps" (select one of the following: "protect from" or "seal out") "wetness." The comments' suggested indications "aids in the temporary relief of minor skin irritations due to (associated with) diaper rash" and "for the temporary protection of minor skin irritation due to (associated with) diaper rash" have been incorporated in the above indications statement. The agency believes that the indication "protects chafed skin" is more informative to consumers than the comments' suggestions of "protects skin" or just "protects."

In the tentative final monograph for OTC skin protectant drug products, the agency proposed to define a skin protectant as a drug which protects injured or exposed skin or mucous membrane surface from harmful or annoying stimuli. (See proposed § 347.3(a), 48 FR 6820 at 6832.) Wetness which contributes to diaper rash could be considered as "annoying stimuli" within this definition. Therefore, the claim "protects and helps seal out wetness" has been incorporated in the Category I indications for skin protectant ingredients for diaper rash. However, "sealing out germs" is a claim for which more testing is needed because there is a lack of evidence that skin protectant active ingredients perform this function.

Claims related to healing, e.g., "promotes healing," and wound healing aids are classified as Category III in the tentative final monograph for OTC skin protectant drug products (48 FR 6831) and in the tentative final monograph for OTC anorectal drug products (53 FR 30756 at 30765; August 15, 1988). The claim "promotes healing" has not been demonstrated in clinical studies for any ingredient contained in OTC diaper rash drug products. Data are needed to establish the effectiveness of any ingredient in diaper rash drug products for this claim. Therefore, this claim is not being included in the indications for diaper rash drug products at this time and is being classified in Category III.

Likewise, none of the proposed Category I ingredients for OTC diaper rash drug products have been shown to relieve inflammation of infants' skin due to diaper rash. Therefore, this claim also is not being included in the indications for diaper rash drug products at this time and is being classified in Category III.

The agency also stated in the tentative final monograph for OTC skin protectant drug products that it considered the terms "soothes" and "rubbing" to be cosmetic claims in the context of skin protectant products. (See 48 FR 6820 at 6828, comment 22.) Accordingly, these terms are not included in the indications for diaper rash drug products.

6. Two comments recommended the following warnings for products used for either the treatment or prevention of diaper rash: "for external use only," "avoid contact with the eyes," and "discontinue use if symptoms persist for more than seven days and consult a physician."

The agency agrees that the three warnings recommended by the comments are applicable to OTC diaper rash drug products. The warnings "for external use only" and "avoid contact with the eyes" are regularly included in the labeling for topical drug products and were proposed in § 347.50(c)(1) and (2) of the tentative final monograph for OTC skin protectant drug products (48 FR 6820 at 6832). The comments' recommended warning regarding the time period for self-treatment is already covered by the warning proposed in 347.50(c)(3) of the tentative final monograph for OTC skin protectant drug products, which reads as follows: "If condition worsens or does not improve within 7 days, consult a doctor." In addition, the general warnings in § 330.1(g) will be required, i.e., "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."

7. Two comments recommended the following directions for products used for either the treatment or prevention of diaper rash: "Apply liberally as often as necessary."

The agency agrees that the directions recommended by the comments are appropriate for skin protectant drug products used for the treatment and prevention of diaper rash. Most of the drug products marketed for the treatment or prevention of diaper rash contain one or more Category I active ingredients that were included in the tentative final monograph for OTC skin protectant drug products for which the agency proposed the directions: "Apply liberally as often as necessary." (See 48 FR 6833.) If there is a need for limiting the frequency or the amount of application of a specific ingredient for safety reasons, that limitation will be reflected in the directions for that specific ingredient.

Based on the Panel's statement that most diaper rash treatments help by protecting the skin, acting as a physical barrier to irritants, and absorbing or adsorbing moisture (47 FR 39436 at 39440) and based on the labeling of a number of currently marketed OTC diaper rash drug products, the agency believes that consumers should also be informed to "apply [the product] with each diaper change and especially at bedtime or anytime when exposure to wet diapers may be prolonged." In addition, based on information from standard texts (Refs. 1 through 5), the labeling of some currently marketed OTC diaper rash drug products (Refs. 6 and 7), numerous articles in the literature (Refs. 8 through 13), and the Miscellaneous External Panel's statement in its discussion on diaper rash that mild diaper rash responds to very frequent diaper changes and cleansing with water (47 FR 39440), the agency has determined that the following general statement would be useful in the directions for products labeled both for prevention and treatment of diaper rash: "Change wet and soiled diapers promptly, cleanse the diaper area, and allow to dry."

Based on numerous reports of toxic episodes resulting from inhalation of powders (see comment 28 below), and recommendations in the literature to shake the powder directly into the diaper or into the hand away from the child's face (Refs. 8 and 12), the agency believes the following information should be included in the directions for powder products: "Apply close to the body away from child's face. Carefully shake the powder into the diaper or into the hand and apply to diaper area." The agency tentatively concludes that these additional statements in the directions will provide consumers with more informative directions for safely and effectively using powder diaper rash drug products.

Based on the above, the agency is proposing the following directions for use in 347.50(d)(4) of this tentative final monograph: (i) *For all products.* "Change wet and soiled diapers promptly, cleanse the diaper area, and allow to dry. Apply" (select one of the following: "ointment," "cream," "powder," or "product") "liberally as often as necessary, with each diaper change, and especially at bedtime or anytime when exposure to wet diapers may be prolonged." (ii) *For powder products only.* "Apply powder close to the body away from child's face. Carefully shake the powder into the diaper or into the hand and apply to diaper area."

The agency also notes that should the final monograph provide for a diaper rash drug product containing a skin protectant active ingredient and Category I topical active ingredient(s) from another class, e.g., an antimicrobial, antifungal, or external analgesic, with a specific time interval or specified quantity for application, then the labeled frequency of application or the amount to be applied of the combination product would not be "liberally as often as necessary." In such situations, the directions for applying the product would not be allowed to exceed the maximum limit established for any ingredient in the product.

References

(1) Smith, G.H., "Diaper Rash and Prickly Heat Products," in "Handbook of Nonprescription Drugs," 7th Ed., American Pharmaceutical Association, Washington, pp. 605–614, 1982.

(2) Weston, W.L., "Practical Pediatric Dermatology," 1st Ed., Little, Brown and Co., Boston, pp. 51–53, 1979.

(3) Weinberg, S., and R.A. Hoekelman, "Pediatric Dermatology for the Primary Care Practitioner," 1st Ed., McGraw-Hill, New York, p. 121, 1979.

(4) Barnett, G., "Baby Toiletries," *in* "Cosmetics Science and Technology," 2d Ed., Wiley-Interscience, New York, pp. 121–135, 1972.

(5) Zimmerman, D.R., "Diaper-Rash Medications," *in* "The Essential Guide to Nonprescription Drugs," 1st Ed., Harper and Row, New York, pp. 228–237, 1983.

(6) Huff, B.B., editor, "Physicians Desk Reference for Nonprescription Drugs," 10th Ed., Medical Economics Co., Inc., Oradell, NJ, pp. 573–574, 682, 1989.

(7) Current labeling for Johnson and Johnson Baby Powder, in OTC Volume 06DRSTFM, Docket No. 78N–021D, Dockets Management Branch.

(8) Brown, M.S., "Over-the-Counter Drugs for Skin Disorders Part 3: Aids for Heat and Diaper Rash," Nurse Practitioner, July–August: 28–30 and 36, 1977.

(9) Sadik, F., "OTC Products for Diaper Rash and Prickly Heat," Journal of American Pharmaceutical Association, 1:19–24, 1970.

(10) Williams, M.L.K., "How I Treat Diaper Rashes," Medical Times, 108:50–53, 1980.

(11) Schanzer, M.C., and J.K. Wilkin, "Diaper Dermatitis," American Family Physician, 25:127–132, 1982.

(12) Gossel, T.A., "Diaper Dermatitis," U. S. Pharmacist, September: 34–40, 1984.

(13) Leyden, J.J., "Diaper Dermatitis," Dermatologic Clinics, 4:23–28, 1986.

C. Comment on Previously Classified Skin Protectant Active Ingredients

8. One comment noted that the reopenings of the administrative record to include the Miscellaneous External Panel's findings on drug products used for diaper rash treatment did not include any Category I ingredients or labeling for this drug category. The comment recommended that those Category I skin protectant active ingredients that ameliorate skin irritation should be listed as Category I agents for diaper rash. The comment asserted that the Miscellaneous External Panel believed that the use of adsorbents, absorbents, astringents, demulcents, emollients, lubricants, and wound healing aids provide mechanical or physical protection which may prevent further irritation associated with diaper rash (47 FR 39436 at 39439).

The agency agrees with the comment that the physical or mechanical protection afforded by skin protectant ingredients is useful in the prevention and treatment of diaper rash. In the advance notice of proposed rulemaking for OTC anorectal drug products (45 FR 35576; May 27, 1980), the Advisory Review Panel on OTC Hemorrhoidal Drug Products (Hemorrhoidal Panel) stated its conclusion that protectants alone or in combination are of therapeutic value by providing a physical barrier that prevents irritation of anorectal tissue. That Panel further stated its belief in the concept of protectants providing a physical barrier over anorectal tissue and preventing further insult, and that the barrier effect of protectants is supported by data indicating that infant perianal skin is afforded significant protection against diaper wetness by the application of a continuous film of petrolatum to the skin in the diaper area (45 FR 35576 at 35627). The agency agrees with the Panel that skin protectants that provide a protective barrier would be useful in either preventing diaper rash or preventing further irritation in the case of an existing diaper rash. The agency also believes that because moisture plays a large part in the development of diaper rash irritation, skin protectant ingredients that absorb or adsorb moisture offer a rational approach to both the prevention or treatment of diaper rash.

The Topical Analgesic Panel, which evaluated skin protectant active ingredients, recommended the following as Category I skin protectant ingredients for use on adults, children, and infants, without any age restrictions: allantoin, calamine, cocoa butter, corn starch, dimethicone, kaolin, petrolatum, sodium bicarbonate, zinc carbonate, and zinc oxide (43 FR 34628 at 34634 through 34642; August 4, 1978). In the tentative final monograph for OTC skin protectant drug products, the agency tentatively deleted corn starch from the skin protectant monograph until diaper rash products were reviewed (48 FR 6820 at 6828). The agency's comments on the use of corn starch in the prevention and treatment of diaper rash appear in comment 18 below. Sodium bicarbonate was transferred by the agency to the external analgesic rulemaking for its antipruritic label claims (48 FR 6830). However, the diaper rash uses of sodium bicarbonate are now being considered in the skin protectant rulemaking and are discussed in comment 27 below.

Because the Topical Analgesic Panel did not specifically review skin protectant ingredients for their use in the prevention or treatment of diaper rash, the agency has evaluated those Category I ingredients that have been used in diaper rash drug products. Of the ingredients discussed above, allantoin, calamine, dimethicone, kaolin, petrolatum, and zinc oxide have an extensive marketing history for the prevention or treatment of diaper rash (Refs. 1 through 4). The agency is not aware of any marketing history for the ingredients cocoa butter or zinc carbonate in products used for diaper rash. Therefore, the agency is proposing those two ingredients as Category III for this specific skin protectant use.

The Topical Analgesic Panel also recommended that four Category I skin protectant ingredients be restricted in their use on children. The Panel recommended the warning "Do not use on children under 2 years of age without consulting a physician," for shark liver oil and zinc acetate (43 FR 34628 at 34640 and 34641). For the ingredients aluminum hydroxide gel and glycerin, the Panel recommended the warning "Do not use on children under 6 months of age without consulting a physician," (43 FR 34634 and 34638). The agency included the warnings for the ingredients aluminum hydroxide gel, glycerin, and zinc acetate in the tentative final monograph for OTC skin protectant drug products (48 FR 6820 at 6833) and deferred a decision on limiting the use of shark liver oil as a skin protectant for the treatment of diaper rash, pending completion of its evaluation of diaper rash products (48 FR 6825). The agency's recommendations on the use of shark liver oil for the treatment of diaper rash are discussed below in this comment.

No data have been submitted to the agency on the use of aluminum hydroxide gel or zinc acetate for the prevention or treatment of diaper rash. In addition, the agency is not aware of any safety data supporting the use of these ingredients on infants. Accordingly, these ingredients are not included as Category I diaper rash ingredients and are classified in Category III.

The Topical Analgesic Panel recommended that 20 to 45 percent glycerin not be used on children under 6 months of age. The agency has received no data in this rulemaking, and is not aware of any data, supporting the safe use of glycerin at this concentration on children under 6 months of age. Therefore, the agency is classifying 20 to 45 percent glycerin in Category III for safety for use as a skin protectant in the prevention or treatment of diaper rash.

The agency received one submission for a combination diaper rash product containing an antimicrobial ingredient (0.1 percent methylbenzethonium chloride), 17.5 percent petrolatum, and 12 percent glycerin as active ingredients (Ref. 5). The data included a study by Niedelman and Bleier using the product for the treatment of diaper rash (Ref. 6). As part of the study, a patch test was performed using the product on 50 infants and children. The infants were divided into three groups and ointment was applied to the back or arm and covered with a half-inch square gauze covered with wax paper and held in place by adhesive tape. In the first group the patch was removed after 24 hours, in the second group after 48 hours, and in the remaining group after 72 hours. The patch test yielded no evidence of sensitivity to the ointment.

In another study by Bleier and Niedelman, 90 infants were studied to determine the safety and effectiveness of the above antimicrobial ointment in the treatment of diaper rash (Ref. 7). The infants, diagnosed as having diaper rash of varying degrees of severity (mild to severe), were divided into two groups. Fifty-eight infants received the antimicrobial ointment and a control group of 32 infants received the base ointment containing 12 percent glycerin and petrolatum. During the treatment study period the authors noted no systemic toxicity, local irritation, or primary or secondary sensitivity in either group.

Lipschutz and Fischer reported similar observations in their study using the same ointment on 100 infants studied over a 3-month period (Ref. 8). Alternate infants were treated with the antimicrobial ointment or the base

containing 12 percent glycerin and petrolatum. The ointment was applied after each diaper change and upon retiring for the night (an average of seven times a day) and no demonstrable toxicity or allergenicity of the ointment was noted. However, because the ages of the infants in the above studies were not specified, no conclusions on the safety of the use of 12 percent glycerin on infants under 6 months of age can be made.

Further, the Panel recommended glycerin at a concentration of 20 to 45 percent as an effective Category I skin protectant (43 FR 34628 at 34648), and the data included in the submission do not demonstrate the effectiveness of the lower concentration of glycerin for the treatment or prevention of diaper rash.

The studies by Bleier and Niedelman (Ref. 7) and Lipschutz and Fischer (Ref. 8) were designed to demonstrate the contribution of the antimicrobial ingredient to the product's effectiveness. No conclusions concerning glycerin's contribution to the effectiveness of the product can be made because glycerin is in combination with petrolatum, another Category I skin protectant ingredient, and both ingredients are present in the placebo and the tested product. Although Niedelman and Bleier (Ref. 6) studied the effectiveness of the Product on 107 infants with diaper rash, they used the complete formulation containing petrolatum, 12 percent glycerin, and the antimicrobial ingredient, and no controls were used. Accordingly, 12 percent glycerin is classified in Category III for safety and effectiveness for use in the treatment and prevention of diaper rash.

In response to the advance notice of proposed rulemaking for OTC skin protectant drug products, the agency received a comment (Ref. 9) opposing the Topical Analgesic Panel's recommendation against using shark liver oil on children under two years of age. The comment argued that the Panel gave no reason for limiting the use of this ingredient on children under 2 and failed to mention that a product containing shark liver oil specifically labeled for use for diaper rash was submitted (Ref. 10). The submission contains a summary of a diaper rash study conducted by Minsky. The study compared an ointment containing 2,000 units of live yeast cell derivative (LYCD) and 3 percent shark liver oil to an undescribed placebo on 54 newborns with peri-rectal diaper rash. All cases had erythema plus either vesiculation, papulation, or excoriation. The infants were divided into a test group of 29 infants treated with the LYCD-shark liver oil combination and a control group of 25 infants treated with the placebo. The comment also cited a study by Grayzel, Heimer, and Grayzel on the value of cod liver oil in the treatment of various dermatoses in infants and adults in support of the safe topical use of shark liver oil on children under the age of two (Ref. 11).

The agency has reviewed the submission (Ref. 10) and the studies mentioned above and determined that the data are insufficient to demonstrate the safe topical use of shark liver oil on children under 2 years of age. In the Minsky study (Ref. 10), 86 percent of the infants in the test group were cured or improved as opposed to 76 percent in the control group. No adverse reactions to either treatment were noted. The lack of any adverse reactions in the 29 infants in the test group is not considered sufficient data to support the safe use of this ingredient for the treatment of diaper rash in children under 2 years of age.

The study by Grayzel, Heimer, and Grayzel (Ref. 11) investigated the effects of cod liver oil in an ointment or lotion base on various dermatoses in 295 infants and children and 56 adults. During the course of the study, no evidence of sensitivity or dermatitis attributable to the ointment or lotion was noted. However, because the amount of cod liver oil in the preparations used in the study is not specified, no comparison to shark liver oil can be made. Further, while cod liver oil and shark liver oil are both sources of vitamins A and D (Refs. 12 and 13), they do not contain the same amounts of either vitamin and, therefore, cannot be considered interchangeable. Accordingly, shark liver oil is classified in Category III for safety for use in the treatment and prevention of diaper rash. The agency's comments on the use of cod liver oil for the prevention or treatment of diaper rash appear in comment 14 below. The agency's comments on the use of vitamins A and D for diaper rash appear in comment 29 below.

Based on the discussion above, the agency is proposing that the following skin protectant ingredients be classified as Category I for the prevention and treatment of diaper rash: allantoin, calamine, dimethicone, kaolin, petrolatum, white petrolatum, and zinc oxide. The agency is proposing that aluminum hydroxide gel, cocoa butter, glycerin, shark liver oil, zinc acetate, and zinc carbonate be classified as Category III for this use.

References

(1) Smith, G.H., "Diaper Rash and Prickly Heat," in "Handbook of Nonprescription Drugs," 6th Ed., American Pharmaceutical Association, Washington, pp. 427–429, 1979.

(2) "Kastrup, E.K., editor, "Topical Diaper Rash Products," in "Facts and Comparisons," J. B. Lippincott Co., St. Louis, p. 563, August 1987.

(3) Brown, M.S., "Over-the-Counter Drugs for Skin Disorders Part 3: Aids for Heat and Diaper Rash," Nurse Practitioner, 2:28–30, 36, and 41, 1977.

(4) OTC Volumes 160021, 160027, 160040, 160041, 160053, 160077, 160150, 160242, 160245, and 160421.

(5) OTC Volume 160243.

(6) Niedelman, M.L., and A. Bleier, "Ammonia Dermatitis: Treatment with Diaperene Chloride Ointment," Journal of Pediatrics, 37:762–764, 1950.

(7) Bleier, A., and M.L. Niedelman, "Ammonia Dermatitis: Comparative Study of Diaperene® Chloride Ointment," Archives of Pediatrics, 69:445–449, 1952.

(8) Lipschutz, A., and C. Fischer, "Methylbenzethonium Chloride in the Care of Skin of Infants and Children," American Journal of Diseases of Children, 89:596–598, 1955.

(9) Comment No. C00006, Docket No. 77N–0021, Dockets Management Branch.

(10) OTC Volume 060113.

(11) Grayzel, H.G., C.B. Heimer, and R.W. Grayzel, "The Value of a Cod Liver Oil Ointment and Cod Liver Oil Lotion in the Treatment of Dermatoses," New York State Medical Journal, October: 2233–2237, 1953.

(12) "The United States Pharmacopeia XXII—The National Formulary XVII," United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 344–345, 1989.

(13) Wade, A., "Martindale. The Extra Pharmacopoeia," 27th Ed., The Pharmaceutical Press, London, pp. 1097–1098, 1978.

D. Comment on Aldioxa.

9. A submission to the Miscellaneous External Panel (Ref. 1) requested Category I status for a product containing 0.2 percent aldioxa (formerly aluminum dihydroxy allantoinate) for the prevention of diaper rash. Although this ingredient is not included in the currently marketed product (Ref. 2), the original submission was reviewed for background information by the Panel in preparing its statement on diaper rash drug products. The submission included reports on oral toxicity studies of aldioxa in mice, a report on the topical sensitizing and irritating potential of aldioxa in guinea pigs, and reports on the safety of the ingredient in infants and children with varying degrees of dermatitis of the buttocks.

Aldioxa is an aluminum salt of the Category I skin protectant allantoin; it is formed by reacting soluble salts of aluminum with allantoin. The resulting compound has astringent properties

attributable to the aluminum in its chemical composition (Ref. 3). The Topical Analgesic Panel, in discussing the safety of allantoin in its report on OTC skin protectant drug products, cited animal sensitization studies and acute oral toxicity studies in rats in which aldioxa was tested (43 FR 34628 at 34632). Based in part on these studies, the Panel concluded that allantoin is safe in OTC topical drug products (43 FR 34633). However, the Panel did not specifically classify aldioxa as a Category I skin protectant, and the data did not address the safety of using aldioxa on infants' skin under conditions such as those present in the diaper area, e.g., increased moisture and occlusion.

One of the reports included in the submission (Ref. 4) is a clinical evaluation by a practicing physician of a talcum powder containing 0.2 percent aldioxa, magnesium stearate, and silicones. Over a 6-month period, 100 infants and children with weeping eczematous rashes, such as heat rash, diaper rash, and similar inflammations, were treated with the powder. The physician concluded that the powder was nonirritating, nontoxic, nonsensitizing, aided in the prevention of diaper rash, and alleviated and prevented irritation due to chafing. However, the report did not provide any details as to the number of diaper rash cases treated, the method of treatment, and the individual responses to treatment with the aldioxa-containing talcum powder. Further, no evaluation of the contribution of the aldioxa to the effectiveness of the product can be made because the evaluation did not include a talc placebo.

In another clinical evaluation by the same physician (Ref. 5), 70 infants with diaper rash and other weeping eczematous rashes were treated daily with a cream containing 0.75 percent aldioxa. No sensitizing or allergic reactions were noted, and in all cases the irritation cleared completely. The report did not provide any details on the number of diaper rash cases treated, method of treatment, or length of treatment.

A clinical evaluation by another physician of the use of a cream containing 0.75 percent aldioxa in a glyceryl monostearate base on 116 infants is included in the submission (Ref. 6). Seventy of the infants showed no sign of irritation in the diaper area at the time of admission or subsequently during the evaluation. Of the 46 infants who showed some irritation at time of admission, 30 were cured, 6 were not observed for a sufficient period of time, and 10 showed no noticeable change. This report also did not provide any details.

The reports discussed above do not provide sufficient detail to support a Category I classification for 0.2 to 0.75 percent aldioxa used for the prevention or treatment of diaper rash. Accordingly, the agency is classifying 0.2 to 0.75 percent aldioxa in Category III for safety and effectiveness for the prevention or treatment of diaper rash.

REFERENCES

(1) OTC Volume 160357.

(2) Letter from B. Leiro, Stiefel Laboratories, Inc., to L. Geismar, FDA, dated October 23, 1985, in OTC Volume 06DRSTFM, Docket No. 78N-021D, Dockets Management Branch.

(3) Mecca, S.B., "Allantoin and the Newer Allantoinates," located at p. 148 in OTC Volume 160357.

(4) Letter containing clinical evaluation of talc, from F.X. Thomas, to Schuylkill Chemical Co., not dated, located at p. 135 in OTC Volume 160357.

(5) Letter from F.X. Thomas, to Schuylkill Chemical Co., not dated, located at p. 137 in OTC Volume 160357.

(6) High, R., "Clinical Evaluation of a Cream Containing 0.75% Aluminum Dihydroxy Allantoinate in a Glyceryl Monostearate Base for the Treatment of 116 Infants With Varying Degrees of Dermatitis of the Buttocks," summary located at p. 138 in OTC Volume 160357.

E. Comment on Aluminum Acetate

10. One manufacturer submitted data to the Miscellaneous External Panel for two products (a cream and a lotion) containing aluminum acetate as the claimed active ingredient (Ref. 1). The manufacturer stated that the formulation includes the components of a modified Burow's solution and that the products are used to restore the skin to its normal protective acid pH. The labeling states that the products "aid in treatment of diaper rash," and the manufacturer requested that the agency place aluminum acetate in Category I for various indications, including "as an aid in the treatment of diaper rash."

The manufacturer subsequently submitted a comment (Ref. 2) for another product containing aluminum acetate used as a wet dressing and requested that the Panel's recommended indications for aluminum acetate solution in § 348.50(b)(4) be revised to include "a soothing wet dressing for relief of skin irritations caused by conditions such as * * * diaper rash * * *." The comment did not provide any data regarding the use of aluminum acetate for the treatment of diaper rash, but did include a copy of the transcript of the November 7, 1980 meeting of the Miscellaneous External Panel which contained the manufacturer's presentation on the ingredient in solution dosage form for use as a compress.

In its statements on OTC astringent drug products (47 FR 39412 at 39425 and 39436 at 39444; September 7, 1982), the Miscellaneous External Panel recommended that the use of astringents be referred to both the external analgesic and skin protectant rulemakings. The agency's proposals concerning the use of external analgesic ingredients for the treatment or prevention of diaper rash appear elsewhere in this issue of the **Federal Register**. Based on the available information, the agency is proposing that any products labeled for the prevention or treatment of diaper rash should not contain any external analgesic ingredients. Based on the manufacturer's claim that aluminum acetate restores the skin to its normal protective acid pH, the agency is considering this ingredient when used in OTC diaper rash drug products to be a skin protectant (see definition of a skin protectant in § 347.3(a) of the tentative final monograph for OTC skin protectant drug products; 48 FR 6820 at 6832) and thus is addressing its use for the treatment of diaper rash in this document. Other uses of aluminum acetate will be addressed in subsequent publications in the **Federal Register**.

In the Miscellaneous External Panel's report on the skin protectant uses of astringent drug products, the Panel recommended that aluminum acetate solution be Category I as an astringent (47 FR 39436 at 39444). However, the Panel did not include the treatment of diaper rash among its proposed indications for this ingredient. The agency is aware of the recommended use of aluminum acetate solution (Burow's solution) in the treatment of severe diaper rash characterized by acute inflammation with oozing or crusting and in candidal diaper rash (Refs. 3, 4, and 5). However, the agency believes that these severe forms of diaper rash are not amenable to OTC treatment and should be treated by a physician. In addition, the agency is not aware of any data supporting the safe and effective use of aluminum acetate solution in the treatment of simple diaper rash.

The submission (Ref. 1) for the cream and lotion products included information regarding the composition of the skin's "acid mantle" and its importance to the skin's barrier functions (Refs. 6, 7, and 8). However, the submission did not contain any data showing the effects of aluminum acetate

cream or lotion in restoring the "acid mantle" or a normal pH to skin irritated by a diaper rash or any data concerning the safe and effective use of aluminum acetate in any dosage form for the treatment of diaper rash. Data and information are needed to show that aluminum acetate restores the skin in the diaper area to its normal protective acid pH, and that the drug has a role in the treatment or prevention of diaper rash. At the November 7, 1980 meeting of the Miscellaneous External Panel, Dr. Leyden discussed a study in which wet dressings containing aluminum acetate were used on six volunteers with induced poison ivy. The Panel voted to classify Burow's (aluminum acetate) solution in Category I for use as an astringent wet dressing based on years of experience and the results of the study; however, use of the wet dressing for diaper rash was not discussed.

Accordingly, the agency concludes that there are insufficient data available to classify aluminum acetate as safe or effective for the OTC treatment of diaper rash and classifies the ingredient as Category III.

References

(1) OTC Volume 160038.

(2) Comment No. C00038, Docket No. 78N-0301, Dockets Management Branch.

(3) Schanzer, M.C., and J.K. Wilkin, "Diaper Dermatitis," American Family Physician, 25:127-132, 1982.

(4) Williams, M.L.K., "How I Treat Diaper Rashes," Medical Times, 108:50-53, 1980.

(5) Smith, G.H., "Diaper Rash and Prickly Heat Products," in "Handbook of Nonprescription Drugs," 8th Ed., American Pharmaceutical Association, Washington, pp. 643-653, 1986.

(6) Gleeson-White, M.H., "The Skin Flora and the Staphylococcus," in "Progress in the Biological Sciences in Relation to Dermatology," edited by A. Rook, University Press, Cambridge, pp. 155-157, 1960.

(7) Hjorth, N., and S. Fregert, "Contact Dermatitis," in "Textbook of Dermatology," edited by A. Rook, D. Wilkinson, and F. Ebling, F.A. Davis Co., Philadelphia, pp. 238-240, 1968.

(8) Montagna, W., "The Structure and Function of Skin," 2d Ed., Academic Press, New York and London, p. 100, 1962.

F. Comment on Bismuth Subnitrate

11. Three submissions to the Miscellaneous External Panel (Ref. 1) from the same manufacturer included data to support the safe and effective use of a product containing bismuth subnitrate (5.8 percent), zinc oxide, and Peru balsam oil as active ingredients for the treatment of diaper rash. Based on the product's current labeling (Ref. 2), the active ingredients of the products are bismuth subnitrate and zinc oxide. (Peru balsam oil is discussed in comment 25 below.)

A submission from another manufacturer (Ref. 3) included information on a combination product containing nine active ingredients, one of which was bismuth subnitrate. The submission did not include any specific information on the use of bismuth subnitrate for the treatment of diaper rash. Based on the product's current labeling (Ref. 4), the product has been reformulated and no longer contains bismuth subnitrate.

The agency has reviewed the data included in the submissions (Refs. 1 and 3) and concludes that they are not adequate to support the safety and effectiveness of bismuth subnitrate for the treatment of diaper rash. One of the submissions described a patch test that was performed on 200 subjects to determine the presence of primary irritation or allergenicity. The test sites were thoroughly cleansed with ether and the product (containing zinc oxide, bismuth subnitrate, and balsam peru) was applied to the skin and covered with a patch. Waterproof tape was then applied to the patch to assure good contact with the skin, and the patch remained on the skin for 48 hours. The test sites were observed and reactions noted after 48 hours and again after 20 minutes to rule out any mechanical reactions. Fifty of the 200 subjects were then retested to rule out any allergic responses. None of the subjects showed any primary irritation or allergic responses. Based on the results of the test, the investigator concluded that the product is not irritating to the skin when applied topically. However, the patch test does not address the use of this ingredient on macerated infant skin as might be found in the case of diaper rash.

An effectiveness study included in the same submission (Ref. 5) evaluated the use of the product containing bismuth subnitrate, zinc oxide, and balsam peru on 558 infants with perianal dermatitis and/or diaper dermatitis. Of the 558 infants tested, 537 infants showed a clearing of their dermatitis; 21 infants showed no clearing. The amount of data presented is very limited. No information was provided on the severity of the rashes of the infants, frequency of application of the product, or length of treatment. Further, the product tested was a combination product. None of the individual components were studied, and there was no vehicle control; thus, it is impossible to assess the effect that bismuth subnitrate contributed to the results observed.

The Topical Analgesic Panel evaluated the use of bismuth subnitrate for use as an OTC skin protectant ingredient and concluded that the ingredient was not safe or effective for this use (43 FR 34628 at 34642). In discussing the safety of this ingredient, the Panel cited reports of fatalities in infants due to oral ingestion of bismuth subnitrate and classified the ingredient in Category II (43 FR 34642). The agency concurred with the Panel's recommendation in the tentative final monograph for OTC skin protectant drug products (48 FR 6820 at 6831).

The use of bismuth subnitrate as a skin protectant was also evaluated by the Hemorrhoidal Panel (45 FR 35576 at 35636). In discussing the safety of this ingredient, that Panel cited human and animal studies demonstrating absorption of bismuth salts through local application to open surfaces. The Panel concluded that the lesions and ulcerations caused by local application of the ingredient were due to metallic bismuth and that bismuth toxicity can be caused by bismuth subnitrate (45 FR 35637). Of greater concern to the Panel was the possibility of nitrite toxicity due to the conversion of nitrate to nitrite in the presence of bacteria normally found in the colon and rectum. The Panel stated that the signs and symptoms of nitrite intoxication are vomiting, convulsions, dizziness, sleepiness, methemoglobinemia, and cardiac collapse. The Panel concluded that because of the rapid absorption of nitrites across mucous membranes, bismuth subnitrate is not safe for use as an OTC anorectal drug product (45 FR 35637). The Panel further concluded that there was no evidence that bismuth subnitrate is more effective than other protectant ingredients which are not associated with a safety problem and classified it in Category II for safety and effectiveness.

Because the studies discussed above do not demonstrate the safety of bismuth subnitrate for use in diaper rash, the agency tentatively concludes that bismuth subnitrate is not safe for OTC use for the treatment of diaper rash. Further, because the only clinical study submitted to support effectiveness involved a combination product, the contribution of bismuth subnitrate to the effectiveness of the product has not been demonstrated. Accordingly, the agency is classifying bismuth subnitrate in Category II for safety and effectiveness for the treatment of diaper rash.

References

(1) OTC Volumes 160041, 160088, and 160421.

(2) Labeling for product Balmex, sent by Macsil, Inc., to FDA, Division of OTC Drug Evaluation, postmarked October 24, 1986, in

OTC Volume 06DRSTFM, Docket No. 78N–021D, Dockets Management Branch.

(3) OTC Volume 160040.

(4) Letter from J.A. Devaney, The Mentholatum Co., Inc., to L. Geismar, FDA, October 23, 1986, in OTC Volume 06DRSTFM, Docket No. 78N–021D, Dockets Management Branch.

(5) Letter containing evaluation of Balmex Baby Cream from G.Y. Elson to M. Waxman, Macsil, Inc., dated October 1956, in OTC Volume 160041.

G. Comment on Borax and Boric Acid

12. One comment requested that borax and boric acid be classified as "inactive" ingredients in diaper rash drug products. The comment contended that borax and boric acid in diaper rash drug products were inactive as defined in 21 CFR 210.3(b) (7) and (8). The comment stated that it had examined the OTC volumes (Refs. 1 through 10) submitted to the Panel for products containing boric acid and/or borax and these submissions did not disclose any claims for their use as active ingredients. The comment added that these ingredients are not active when used as buffering agents (Refs. 1 and 10), preservatives, or stabilizers (in emulsions) because their role is not to treat diaper rash. The comment noted that the Panel stated at 47 FR 39416 that it did not review any individual ingredients as used in OTC diaper rash drug products. The comment asked whether these ingredients can continue to be used as pharmaceutical necessities in diaper rash drug products.

The agency has reviewed the submissions referred to by the comment and determined that the labeling and information contained in some of them represent boric acid as an active ingredient in four products, three of which were labeled for diaper rash use (Refs. 3, 4, 5, and 10). In evaluating the current formulations of these products, the agency has determined that three of the products have been reformulated to delete the boric acid and the fourth product has been discontinued (Refs. 11, 12, and 13). The agency has surveyed products currently available in the marketplace and identified one additional ointment that contains 5 percent boric acid and is labeled for use in diaper rash (Ref. 14). Boric acid is considered an active ingredient in this product.

A number of OTC advisory review panels have evaluated the safety of boric acid and have found it to be unsafe for use in OTC anorectal, skin protectant, dandruff and seborrheic dermatitis, oral health care, and vaginal (at greater than 1 percent concentration) drug products. Based on these panels' classifications, the agency considers boric acid to be Category II (not generally recognized as safe) as an active ingredient in diaper rash drug products.

The agency is not aware of boric acid or borax being used or of the need to use either as an inactive ingredient to buffer, preserve, or stabilize any OTC diaper rash drug product. The regulations for products regulated by OTC drug monographs state that "the product contains only suitable inactive ingredients which are safe in the amounts administered * * *." (See 21 CFR 330.1(e).) The agency is not aware of any evidence establishing that boric acid or borax is a suitable inactive ingredient for use in OTC diaper rash drug products.

References

(1) OTC Volume 160022.
(2) OTC Volume 160024.
(3) OTC Volume 160040.
(4) OTC Volume 160077.
(5) OTC Volume 160091.
(6) OTC Volume 160093.
(7) OTC Volume 160140.
(8) OTC Volume 160230.
(9) OTC Volume 160233.
(10) OTC Volume 160236.
(11) Comment No. RPT, Docket No. 80N–0476, Dockets Management Branch.
(12) Letter from J.A. Devaney, The Mentholatum Co., Inc., to L. Geismar, FDA, dated October 23, 1986, in OTC Volume 06DRSTFM, Docket No. 78N–021D, Dockets Management Branch.
(13) Letter from A.D. Marcus, Bristol-Myers Products, to Dockets Management Branch, FDA, dated March 11, 1987, coded LET017, Docket No. 78N–021D, Dockets Management Branch.
(14) Smith, C.H., "Diaper Rash and Prickly Heat Products," in "Handbook of Nonprescription Drugs," 8th Ed., American Pharmaceutical Association, Washington, p. 651, 1986.

H. Comment on Casein

13. One manufacturer submitted data to the Miscellaneous External Panel for a combination product for which it listed four active ingredients, one of which was casein (calcium caseinate powder) (Ref. 1). The product was labeled for the treatment and prevention of diaper rash. The submission included a study by Grossman (Ref. 2) who described the product as "an antienzymatic and antibacterial ointment * * * with a casein competitive substrate * * *." However, neither Grossman nor the manufacturer provided any additional information concerning casein (calcium caseinate) in the combination drug product.

Subsequently, the manufacturer submitted the current labeling for the product, and this labeling did not include casein (calcium caseinate powder) as an active ingredient (Ref. 3). Because the agency is not aware of any use of this ingredient as an active ingredient in diaper rash drug products, casein (calcium caseinate) is not being classified in this rulemaking.

References

(1) OTC Volume 160245.
(2) Grossman, L., "A New Specific Treatment for Perianal Dermatitis," Archives of Pediatrics, 71:173–179, 1954.
(3) Letter from C.E. Calcagni, Sterling Drug Inc., to L. Geismar, FDA, dated December 30, 1986, in OTC Volume 06DRSTFM, Docket No. 78N–021D, Dockets Management Branch.

I. Comments on Cod Liver Oil

14. Two comments requested Category I status for cod liver oil used for the treatment and prevention of diaper rash. The comments pointed out that cod liver oil has skin protectant properties and is recognized for its barrier-like action, water insolubility, and emollience. One of the comments (Ref. 1) cited data previously submitted to the Miscellaneous External Panel regarding its combination product containing 13.56 percent cod liver oil and 40 percent zinc oxide in a petrolatum-lanolin vehicle (Ref. 2); submitted a report from a clinical study on this product (Ref. 3) that was referenced in its previous submission (Ref. 2); and requested that its combination product as well as the individual active ingredients and quantities contained therein be classified as Category I for the treatment and prevention of diaper rash. Another drug manufacturer also made a submission on a marketed combination product containing 5 percent cod liver oil (containing natural vitamins A and D), 20 percent zinc oxide, and 0.1 percent methylbenzethonium chloride in a calcium caseinate powder vehicle (Ref. 4). The comments and submissions (Refs. 1 through 4) also included published and unpublished clinical study data regarding the treatment and/or prevention of diaper rash in newborn infants and dermatoses in incontinent, chronically-ill patients.

Cod liver oil was not previously categorized for use as an OTC skin protectant because the agency deferred review of this ingredient to its evaluation of diaper rash drug products. (See the notice of proposed rulemaking for OTC skin protectant drug products, 48 FR 6820 at 6825 comment 12.)

The agency has evaluated the submitted data. In a study by Grayzel, Heimer, and Grayzel (Ref. 5), three combination products containing cod liver oil (concentrations not specified) were tested for four general groups of dermatologic conditions in infants,

children, and adults. A total of 295 infants and children and 56 adults was studied. One subgroup (that included 215 infants and children) having a variety of significant contact dermatitis (as a result of repeated and continuous contact with external irritants such as diarrheal stools, soaked diapers, or ammoniacal urine) was treated with a cod liver oil ointment. Results were rated either as good (indicating return of skin condition to practically normal) or fair (indicating a significant amelioration of skin condition) only if an immediate favorable response occurred within 24 hours, with a maximum effect within 48 hours. The results were good in 164 cases (76 percent), fair in 44 patients (21 percent), and there was no change in skin condition in 7 cases (3 percent). For 153 infants under 1 year of age, the results were good for 111 (72.5 percent), fair for 36 (23.5 percent), and unchanged for 6 (4 percent). The authors concluded that "cod liver oil ointment and cod liver oil lotion offer good topical applications for the treatment of a variety of skin disorders and wounds. They are safe, harmless, * * * may be used without fear of skin sensitivity * * *." (See Ref. 5 page 2237.)

A clinical study (Ref. 3) conducted using a crossover design involved treatment of diaper rash in 45 infants with a product containing cod liver oil in addition to other protectants. The infants had basically untreated diaper rash of at least 12 hours duration immediately prior to admission to the study. Twenty infants had the product applied to the left side but not the right; 25 infants were treated on the right side, but not the left. The product was applied at the beginning of the study and at each diaper change for approximately 24 hours. The severity of the diaper rash was graded prior to application of the product and at the completion of treatment. The investigator concluded that "on the average the treated side was better than the untreated side." Further, no adverse reactions were noted. However, the study does not serve to demonstrate the effect of the individual ingredients in the formulation.

While none of the clinical study data (Refs. 1 through 4) included vehicle controls or showed the contribution of cod liver oil alone, the long history of clinical use of cod liver oil in ointments support its safety and effectiveness as a skin protectant ingredient for use in diaper rash drug products (Refs. 5 through 8). Cod liver oil, when used in combination with other protectants, provides a physical barrier that protects the skin and thus helps to prevent irritation of the diaper area. Lee (Ref. 6) addressed formulations of cod liver oil as follows:

> * * * cod-liver oil alone is not quite sufficient and an added component containing astringent and oligo-dynamic qualities is desirable. * * * Many ointments obtained by simple admixture of ingredients have the defect * * * of melting quickly at body temperature, thus releasing the unpleasant smell of cod-liver oil and soaking through the bandage * * * a cod-liver oil-zinc paste preparation * * * produced the desired effect with a retention of its consistency at body temperature. (Quoted material found on last unnumbered page.)

The agency has surveyed the marketplace and determined that cod liver oil is marketed in a number of products with diaper rash claims (Refs. 8 and 9). The Handbook of Nonprescription Drugs (Ref. 8) identifies four products that contain cod liver oil. As best as the agency can ascertain, cod liver oil is being marketed in diaper rash drug products only in combination with other ingredients, such as lanolin and petrolatum. Based on the various submissions and the Handbook of Nonprescription Drugs, the agency has determined that these products are available at concentrations of 5 to 13.56 percent cod liver oil and that all such products contain more than one skin protectant ingredient for use in the treatment and prevention of diaper rash.

In the rulemaking for OTC anorectal drug products, the Hemorrhoidal Panel classified cod liver oil (50 percent or greater per dosage unit) in Category I for use as a protectant (anorectal agent) (May 27, 1980; 45 FR 35630). The Panel stated that an extensive review of the literature on cod liver oil reveals no adverse effects when applied topically as a protectant. The Panel concluded that the effectiveness of cod liver oil as a protectant is due to its bland and soothing effect associated with its oily nature. In the tentative final monograph for OTC anorectal drug products, the agency affirmed that Panel's Category I classification of cod liver oil and specified that the ingredient may not be used as a sole protectant ingredient but may be used in combination with one, two, or three other protectant active ingredients. (See 53 FR 30756 at 30767; August 15, 1988.)

Based on the agency's market survey discussed above, the agency is not aware of any diaper rash drug products that contain cod liver oil as a single protectant ingredient. Accordingly, the agency is proposing that cod liver oil in diaper rash drug products may be used only in combination with certain other skin protectant active ingredients within the concentrations specified in proposed § 347.10.

Cod liver oil is recognized in the current United States Pharmacopeia/National Formulary (Ref. 10). Cod liver oil U.S.P. is assayed in terms of its vitamin A and cholecalciferol (vitamin D) content and contains in each gram not less than 850 U.S.P. units of vitamins A and 85 U.S.P. units of vitamin D. (One U.S.P. unit is equivalent to one International Unit.) The Hemorrhoidal Panel recommended a maximum daily dose of 10,000 U.S.P. units for vitamin A and 400 U.S.P. units for cholecalciferol per 24 hours (45 FR 35576 at 35630). The agency proposed this dosage for this ingredient in the tentative final monograph for OTC anorectal drug products (53 FR 30756 at 30782) and believes that these maximum daily doses would also be appropriate for diaper rash use of these ingredients.

Considering that cod liver oil contains a minimum of 850 units per gram (g) of vitamin A and 85 units per g of vitamin D, the product with 13.56 percent cod liver oil containing these minimum levels would reach the maximum daily dose with 35 g of product. This quantity exceeds the amounts likely to be used by the average consumer. The Hemmorhoidal Panel assumed an average dose of 2 g for protectants (45 FR 35627). Even if a diaper rash product were applied 10 or more times a day, the maximum daily dose (10,000 U.S.P. units for vitamin A and 400 U.S.P. units for cholecalciferol) being proposed by the agency for this ingredient in this tentative final monograph would not be exceeded. Manufacturers that use cod liver oil containing more than the minimum levels will have the responsibility to formulate and label their product so that this maximum daily dose will not be exceeded.

Based on the Hemorrhoidal Panel's evaluation and the other information stated above, the agency is proposing to classify cod liver oil (5 to 13.56 percent) as Category I for use in OTC diaper rash drug products in this tentative final monograph as follows:

Cod liver oil, in accordance with § 347.20(e), provided that the product is labeled so that the amount of the product that is used in a 24-hour period represents a quantity that provides 10,000 U.S.P. units of vitamin A and 400 U.S.P. units of cholecalciferol.

The agency invites comments and supporting data on the appropriateness of this and other amounts of cod liver oil as an active ingredient in drug products labeled for the prevention and treatment of diaper rash and on this proposal to limit use of this ingredient to

combination skin protectant diaper rash drug products.

Cod liver oil for skin protectant uses other than for diaper rash will be addressed in the final monograph for OTC skin protectant drug products in a future issue of the Federal Register.

References

(1) Comment No. C00030, Docket No. 78N–0021, Dockets Management Branch.
(2) OTC Volume 160021.
(3) Comment No. C00058, Docket No. 78N–0021, Dockets Management Branch.
(4) OTC Volume 160245.
(5) Grayzel, H.G., C. B. Heimer, and R. W. Grayzel, "The Value of Cod Liver Oil Ointment and Cod Liver Oil Lotion in the Treatment of Dermatoses," New York State Journal of Medicine, 53:2233–2237, 1953.
(6) Lee, J.R., "Clinical Facts of Desitin Ointment," reprinted from "International Review of Medicine and Surgery," London, 1939.
(7) Verbov, J., "Common Eruptions in the Napkin Area," The Practitioner, 220:779–784, 1978.
(8) Smith, G.H., "Diaper Rash and Prickly Heat Products," in "Handbook of Nonprescription Drugs," 8th Ed., American Pharmaceutical Association, Washington, pp. 643–653, 1986.
(9) Kastrup, E.K., editor, "Topical Diaper Rash Products," in "Facts and Comparisons," J.B. Lippincott Co., St. Louis, p. 563, August 1987.
(10) "The United States Pharmacopeia XXII—The National Formulary XVII," United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 344–345, 1989.

J. Comments on Colloidal Oatmeal

15. One comment, regarding several products containing colloidal oatmeal as the principal active ingredient, was submitted in response to the publication of the tentative final monograph for OTC external analgesic drug products (February 8, 1983; 48 FR 5852). The comment submitted data and requested that FDA include colloidal oatmeal in the monograph for OTC external analgesic drug products as an ingredient generally recognized as safe and effective for the following indications: "For prompt temporary relief of itchy, sore, sensitive skin due to rashes, eczema/psoriasis, hemorrhoidal and genital irritations, diaper rash, chicken pox, prickly heat, hives, poison ivy/oak, and sunburn."

Elsewhere in this issue of the Federal Register, the agency is addressing one aspect of the comment's request: The antipruritic (anti-itch) use of colloidal oatmeal for diaper rash. The agency will address the antipruritic use of colloidal oatmeal for the other conditions described in the comment in a future Federal Register publication pertaining to the rulemaking for OTC external analgesic drug products. The use of colloidal oatmeal as a skin protectant is discussed in comment 16 below.

16. One comment requested that colloidal oatmeal be included in the skin protectant monograph as a safe and effective ingredient for the claim: "For prompt temporary relief of itchy, sore, sensitive skin due to: * * * diaper rash * * *." The comment based its request on the Miscellaneous External Panel's review of colloidal oatmeal as an antipruritic at that Panel's 23rd meeting on January 29 and 30, 1978. The comment noted that the Panel found colloidal oatmeal at all concentrations to be safe and effective as a bath additive, cleansing bar, and soak for the treatment of dry skin and the resultant itching (Ref. 1).

The comment contended that colloidal oatmeal falls within the Topical Analgesic Panel's definition of a skin protectant, because due to its physical and chemical properties it isolates exposed skin or mucous membrane surface from harmful or annoying stimuli (see proposed § 347.3 at 43 FR 34648). Moreover, the comment added, colloidal oatmeal meets the Panel's criteria described at 43 FR 34630 in that it protects by mechanical or other physical means, is inert, insoluble, finely subdivided, and adsorbs some moisture. The comment stated that colloidal oatmeal that is dispersed in water and applied to the skin deposits particles on the skin and leaves behind an occlusive film barrier that is helpful in protecting skin against irritation and in soothing irritated skin conditions. The comment added that colloidal oatmeal when added to water controls the osmotic pressures of water with respect to the skin and permits adequate water to enter into the stratum corneum. The comment stated that the oatmeal leaves behind a thin occlusive film on the skin and this serves to hold in the adsorbed moisture. The result of this coating is that the skin is protected against irritation. The comment concluded that for these reasons colloidal oatmeal should be classified in Category I as a skin protectant for diaper rash.

The comment's anti-itch claim is discussed in the notice of proposed rulemaking to amend the tentative final monograph for OTC external analgesic drug products published elsewhere in this issue of the Federal Register. The agency concluded that colloidal oatmeal could not be used in an OTC diaper rash drug product bearing an anti-itch claim but could be used in OTC diaper rash drug products bearing only skin protectant claims. In this document, the agency is addressing only skin protectant claims for diaper rash drug products.

The agency agrees that colloidal oatmeal qualifies as a skin protectant because of its barrier-like properties. However, after reviewing the data submitted by the comment (Ref. 2), the agency concludes there is insufficient information to demonstrate that colloidal oatmeal is safe and effective when used as a bath, soak, or cleansing bar for the treatment or prevention of diaper rash. Most of the data that were submitted involved relief of itching due to dry skin conditions. Only one report (Ref. 3) described the use of colloidal emollient baths (colloidal oatmeal impregnated with 35 percent liquid oils) as adjuvant therapy in various pediatric dermatoses including 30 patients with intertrigo and diaper rashes. The article stated that in this bathing procedure some of the bath water is imbibed by the skin tissues, thereby softening the skin. The water is retained in the skin by means of a thin occlusive film of oil which remains on the skin and acts as an effective barrier by retarding the evaporation of water from the skin surface, keeping the stratum corneum hydrated.

In order to evaluate the effectiveness of these colloidal emollient baths, a study was conducted on 152 pediatric patients with various dermatoses associated with dryness of the skin. Thirty of these patients had contact dermatitis, which included intertrigo and diaper rashes. When indicated, other specific medicaments such as corticosteroid and antibiotic preparations were used. It is not clear from the report whether any of these other medicaments were used on the patients with diaper rash. The author reported that the baths of colloidal oatmeal in a super oil form proved to be an excellent adjunct to the therapy used. It was also noted that the baths were used as a routine cleansing and protective measure even after the dermatoses had completely subsided.

For several reasons, the agency does not consider these data adequate to support the use of colloidal oatmeal for the prevention or treatment of diaper rash. First, it is unclear whether the desirable product to use would be colloidal oatmeal or colloidal oatmeal impregnated with 35 percent liquid oils. The comment reports that colloidal oatmeal contains 46 percent carbohydrate, 9 percent oil, 24 percent protein, 8 percent moisture, and a negligible amount of crude fiber. There is no evidence from the data submitted that the product with 9 percent oil will leave a sufficient protective film of oil on the skin. The only data submitted on use of the ingredient on patients with

diaper rash involved the use of the oilated colloidal oatmeal (impregnated with 35 percent liquid oils). It is unclear what these liquid oils are, and what the total "oil" content of this product is.

The agency also has some additional concerns about the use of this ingredient for diaper rash conditions. It is unclear how hydrating the skin in the diaper area (which skin may already be well hydrated from urine) and occluding the skin can aid in treating or preventing diaper rash. The Miscellaneous External Panel, in its discussion of diaper rash, implicated wetness and occlusion in contributing to or worsening diaper rash (47 FR 39436 at 39440). Also, in this tentative final monograph, the agency is proposing the claims "helps protect from wetness" and "helps seal out wetness" for skin protectant drug products used for diaper rash. As discussed in the report (Ref. 3) submitted by the comment, it appears that the colloidal oatmeal could seal in wetness. Accordingly, because of the lack of data demonstrating safety and effectiveness for use for diaper rash, the agency is classifying colloidal oatmeal in Category III for diaper rash. The use of colloidal oatmeal for other skin protectant claims will be addressed in another document related to the rulemaking for OTC skin protectant drug products, to be published in a future issue of the Federal Register.

As noted above, the comment described colloidal oatmeal as containing 46 percent carbohydrate, 9 percent oil, 24 percent protein, 8 percent moisture, and negligible amount of crude fiber. In the tentative final monograph for OTC skin protectant drug products for poison ivy, poison oak, poison sumac, and insect bites (54 FR 40808 at 40810), the agency stated that it does not find this information to be an adequate public standard for colloidal oatmeal. There are no publicly available chemical standards that can be used by any manufacturer who wishes to utilize colloidal oatmeal as an ingredient in its product(s). In order for colloidal oatmeal to be generally recognized as safe and effective as a skin protectant, the agency must have sufficient data on the composition and concentration of the different constituents and the quantity (range) of each that is contained in marketed products. For an ingredient or mixture to be included in an OTC drug final monograph, it is necessary to have publicly available chemical information that can be used by all manufacturers to determine that the ingredient is appropriate for use in their products. In he tentative final monograph for OTC skin protectant drug products for poison ivy, poison oak, poison sumac, and insect bites (54 FR 40810), the agency stated that it would be appropriate for interested parties to develop with the United States Pharmacopeial Convention appropriate standards for the quality and purity of colloidal oatmeal. Should interested parties fail to provide necessary information so that an appropriate standard may be established, colloidal oatmeal will not be included in a final monograph.

References

(1) Summary Minutes of the Twenty-Third Meeting of the Advisory Review Panel on OTC Miscellaneous External Drug Products, January 29 and 30, 1978, Dockets Management Branch.
(2) OTC Volumes 160069 and 160070.
(3) Dick, L. A., "Colloidal Emollient Baths in Pediatric Dermatoses," Archives of Pediatrics, 75:506–508, 1958.

K. Comments on Corn Starch

17. In response to the tentative final monograph for OTC skin protectant drug products published in the Federal Register of February 15, 1983 (48 FR 6820), one comment disagreed with the agency's 97 percent limitation of the concentration of corn starch "to allow for formulation with a dessicant or other pharmaceutical necessity." The comment contended that the agency's prescribing the method of formulation of active ingredients is inappropriate where evidence of safety or efficacy concerns is nonexistent. The comment noted that formulations containing corn starch at levels approaching 100 percent have been successfully marketed. The comment recommended that the agency drop all formulation-related constraints on concentration levels when corn starch is reviewed for use in diaper rash drug products and extend the concentration range to provide for products containing 10 to 100 percent. However, the comment did acknowledge that formulations containing 100 percent corn starch do not now exist.

The Topical Analgesic Panel recommended a concentration range of 10 to 85 percent for the topical application of corn starch (43 FR 34628 at 34636). The Panel noted, however, that because corn starch is so absorptive of water, a sticky mass may form when it is used alone (i.e., at 100 percent). Therefore, another finely dispersed dessicant is usually incorporated in a formulation for use as an absorbent.

In response to comments received on the Panel's recommendation, the agency tentatively agreed in the tentative final monograph for OTC skin protectant drug products that an increase to 97 percent rather than 100 percent would be appropriate to allow for formulation with a dessicant or other pharmaceutical necessity (48 FR 6820 at 6826). The agency did not include corn starch in the tentative final monograph because its primary OTC drug use seemed to be in diaper rash drug products. The agency also deferred its proposal on the appropriate upper concentration limit for corn starch until its use in diaper rash drug products was reviewed.

Corn starch is listed among the ingredients marketed for diaper rash in the Miscellaneous External Panel's statement on OTC drug products for the treatment of diaper rash (47 FR 39436 at 39439). The agency reviewed the submissions on diaper rash drug products that contain corn starch as an active ingredient and found the following concentrations in different dosage forms: 9.52 percent in an ointment (Ref. 1), 41 percent in a powder (Ref. 2), and 96 percent in another powder (Ref. 3). Another powder product (labeled for the prevention and treatment of diaper rash, among other claims) was submitted to the Topical Analgesic Panel (Ref. 4). The submission states that this product contains 71.4 percent corn starch. The agency has been informed that the product currently contains 83.2 percent corn starch (Ref. 5). The agency also notes that in the tentative final monograph for OTC skin protectant drug products the change to a higher concentration was in response to a comment whose own product contained 96 to 97 percent corn starch. The current labeling for this same product shows that it now contains 98 percent corn starch (Ref. 6).

The agency continues to believe that without a dessicant or other pharmaceutical necessity, corn starch (at a 100 percent concentration) is likely to form a sticky mass when it absorbs moisture. The comment did not provide any data showing that 100 percent corn starch would not form a sticky mass when it absorbs moisture. As the comment pointed out, formulations containing 100 percent corn starch do not now exist. If appropriate data are submitted, the agency will then consider raising the allowable concentration to 100 percent. In the interim, based on the 98 percent product that has apparently been marketed without any problems, the agency proposes to increase the upper concentration limit for corn starch from 97 percent to 98 percent. This revised upper concentration would still allow for formulation of products with a dessicant or other pharmaceutical necessity to prevent a sticky mass from

forming. Accordingly, based on the above, the agency is proposing that corn starch at a concentration of 10 to 98 percent be classified in Category I for the treatment and prevention of diaper rash.

Although "corn starch" has been used as the name for the starch used in diaper rash products, "topical starch" is the official title used in the United States Pharmacopeia XXII (Ref. 7). Therefore, "topical starch" is the name proposed for this ingredient in this tentative final monograph.

References

(1) OTC Volume 160040.
(2) OTC Volumes 160077 and 160091.
(3) OTC Volumes 160242 and 160427.
(4) OTC Volume 060137.
(5) Memorandum of telephone conversation between D. Whittington, Plough Inc., and L. Geismar, FDA, dated July 8, 1987, in OTC Volume 06DRSTFM, Docket No. 78N–021D, Dockets Management Branch.
(6) Current labeling for Johnson & Johnson Baby Powder, in OTC Volume 06DRSTFM, Docket No. 78N–021D, Dockets Management Branch.
(7) "The United States Pharmacopeia, XXII—The National Formulary XVII," United States Pharmacopeial Convention, Inc., Rockville, MD., p. 1276, 1989.

18. Two submissions to the Miscellaneous External Panel (Ref. 1) contained data on the safety and effectiveness of a product containing corn starch as an active ingredient for the prevention and treatment of diaper rash. Other submissions (Refs. 2 and 3) contained studies on corn starch and Candida albicans (*C. albicans*). Two other submissions (Refs. 4 and 5) were for products in which corn starch was an inactive ingredient.

In the advance notice of proposed rulemaking for OTC skin protectant drug products (August 4, 1978; 43 FR 34628), the Topical Analgesic Panel recommended corn starch as safe and effective for OTC use as a skin protectant based on its absorbent properties. The Panel indicated that there are no reported incidents of adverse effects to the topical application of corn starch and that its absorptive properties surpass any powder described in the official compendia. The Panel classified corn starch in Category I at a concentration range from 10 to 85 percent (43 FR 34635 to 34636).

The agency did not include corn starch in the tentative final monograph for OTC skin protectant drug products (February 15, 1983; 48 FR 6820), but deferred classifying it until its use in diaper rash drug products (the primary OTC use) was reviewed (48 FR 6828). However, in response to a comment, the agency tentatively raised the concentration limit to 97 percent. (See 48 FR 6826 comment 15.)

In the Miscellaneous External Panel's statement on OTC diaper rash drug products, the use of corn starch for diaper rash was referred to the rulemaking for OTC skin protectant drug products because these products provide mechanical or physical protection and may prevent further skin irritation associated with diaper rash (September 7, 1982; 47 FR 39436 at 39439). Although the Panel did not discuss corn starch in its statement, it did discuss this ingredient at its 30th meeting, on March 12, 1979 (Ref. 6), and expressed concern about corn starch promoting the growth of *C. albicans* when used on the skin of the diaper area and thus contributing toward skin infections. Others (Refs. 7, 8, and 9) also report that corn starch serves as a culture medium for microorganisms, especially *C. albicans*, an organism that is part of the normal colonic flora. However, Honig (Ref. 9) reports that an unpublished study by Leyden indicates that corn starch applied to human skin does not serve as a culture medium for *C. albicans* and does not promote or aggravate dermatitis due to *C. albicans*.

The unpublished studies by Leyden (Refs. 2 and 3) were submitted to the Panel to support the safety of 100 percent corn starch for use as a diaper rash powder. In one study (Ref. 2), three sites on each forearm of six subjects were inoculated with *C. albicans*. After the inoculum dried, the sites on one forearm were covered with plastic film and the edges sealed with tape. The sites on the other forearm were covered with 150 milligrams (mg) of corn starch (used for cooking purposes), covered with plastic film, and sealed with tape. Quantitative cultures and clinical assessments were obtained 24 hours after the sites were prepared. The sites treated with corn starch did not show increased numbers of *C. albicans*, which could occur if the organism was using corn starch as a nutrient. There was a definite trend for less *C. albicans* and aerobic organisms on the sites treated with corn starch. This reduced growth may have been due to a drying effect of the corn starch because of its absorption of water. In a second similar study (Ref. 3) with nine subjects, 100 percent corn starch U.S.P. was compared with a product containing 96.29 percent corn starch U.S.P., 3.50 percent magnesium carbonate N.F., 0.059 percent methylbenzethonium chloride, and 0.15 percent perfume, and was also compared with untreated controls. The conclusion from the two studies that were conducted under exaggerated conditions was that corn starch did not act as a nutrient for *C. albicans* on human skin and would not promote or aggravate dermatitis caused by this organism.

The animal and human safety studies included in two of the submissions (Ref. 1) were for the total formulation of a product in which corn starch, at a concentration of 41 percent, was one of the active ingredients. The studies were not designed specifically to show the safety of corn starch as a single active ingredient or at a 100 percent concentration.

In another submission (Ref. 4), the manufacturer stated that, based on references it cited (Refs. 10 through 13), there are no known toxic effects when corn starch was administered externally. Corn starch was present in the ointment product at a concentration of 9.52 percent. Although listed as an active ingredient in the submission, the product's label did not claim that it is active. In fact, the efficacy data in the submission stated that the starch provides a stiffer consistency (to aid stability when the product is subjected to changes in atmospheric temperatures) and smoothness to the ointment. The agency finds these to be characteristics of a pharmaceutical necessity, and not an active ingredient. The agency has reviewed the references cited in the submission and determined that they do not contain any statements about there being no known toxic effects when corn starch is applied externally, and especially no statements about use in diaper rash.

The agency concludes that if the proposed directions for diaper rash drug products are followed (see comment 7 above), (that is, to change wet and soiled diapers promptly, cleanse the diaper area, and allow to dry), this will help reduce the number of microorganisms in the diaper area, including *C. albicans*. Gossel (Ref. 8) states that moisture enhances microbial growth and increases the chance of rash. The Topical Analgesic Panel noted that corn starch allows for enhanced evaporation of moisture from the skin by increasing the surface area available, and microorganisms are absorbed and suspended by the corn starch (43 FR 34628 at 34636). The evaporation of moisture and the absorption of microorganisms help reduce the growth of microorganisms in the diaper area because many microorganisms require moisture to survive. Accordingly, the agency tentatively concludes that corn starch is safe for use in diaper rash drug products.

Regarding the effectiveness of corn starch, one submission indicated that it

was official in the U.S.P. as a dusting powder, that it prevents friction, is absorptive (drying the skin by taking up water and toxic materials), and it has a cooling effect (provides extra surface area for loss of heat). Like the safety data, the effectiveness studies in these submissions (Ref. 1) apply to the total product in which corn starch was just one of the ingredients. Most of the studies were designed to show the effectiveness of the antimicrobial ingredient in the product.

Based on the Topical Analgesic Panel's Category I classification of corn starch as a safe and effective skin protectant, the Miscellaneous External Panel's recommendation of skin protectants such as corn starch for diaper rash, the additional data reviewed, and the lack of known adverse reactions resulting from its topical use, the agency is classifying corn starch in Category I for the prevention and treatment of diaper rash. As discussed in comment 17 above, the Category I concentration range is from 10 to 98 percent.

References

(1) OTC Volumes 160077 and 160091.
(2) OTC Volume 160362.
(3) OTC Volume 160427.
(4) OTC Volume 160040.
(5) OTC Volume 160242.
(6) Transcript of Proceedings of the Advisory Review Panel on OTC Miscellaneous External Drug Products, March 12, 1979, pp. 225 and 236–237, in OTC Volume 06DRSTFM, Docket No. 78N–021D, Dockets Management Branch.
(7) Arndt, K., "Diaper Rash," in "Manual of Dermatologic Therapeutics—with Essentials of Diagnosis," 2d Ed., Little, Brown and Co., Boston, 1978.
(8) Gossel, T.A., "Diaper Dermatitis," U. S. Pharmacist, September: 34–40, 1984.
(9) Honig, P.J., "Diaper Dermatitis," Postgraduate Medicine, 74:79–88, 1983.
(10) "The United States Pharmacopeia," 18th Revision, United States Pharmacopeial Convention, Inc., Rockville, MD, 1970.
(11) "The National Formulary," 13th Ed., American Pharmaceutical Association, Washington, 1940.
(12) Osol, A., R. Pratt, and M.D. Altschule, editors, "The United States Dispensatory," 26th Ed., J.B. Lippincott Co., Philadelphia, 1967.
(13) Krantz, J.C., and C.J. Carr, "Pharmacological Principles of Medical Practice," 5th Ed., Williams and Wilkins, Baltimore, 1961.

L. Comments on Dexpanthenol.

19. Two drug manufacturers made submissions to the Miscellaneous External Panel (Refs. 1, 2, and 3) on their products containing dexpanthenol and requested Category I classification for the products.

The submissions were reviewed by the Panel in preparing its statement on diaper rash drug products, but the Panel did not classify any of the ingredients in these products. (See 47 FR 39436.) One manufacturer's product was a cream containing vitamin A palmitate, vitamin D_2, dexpanthenol (5 percent), and vitamin E (as dL-alpha-tocopheryl acetate) and was labeled for "temporary relief of irritation, pain, and itching in * * * diaper rash * * *," (Ref. 1). The manufacturer of this product subsequently advised FDA that its product had been repositioned as a cosmetic and requested that its submission (Ref. 1) be deleted from consideration as an OTC drug product (Ref. 4). Accordingly, the submission is no longer being considered in this rulemaking.

The second manufacturer's products (marketed as a cream or lotion) contained dexpanthenol (2 percent), menthol, and camphor and were labeled "for relief of itching and discomfort in minor skin disorders * * *. Useful in diaper rash * * *," (Ref. 2). The manufacturer has advised FDA that its lotion product is no longer marketed, and provided a copy of the current labeling for the cream product (dexpanthenol 2 percent), which states that it "relieves skin itching and irritation; aids healing; for use in * * * diaper rash * * *," (Ref. 5).

The agency has reviewed the submissions for this product, which included an unpublished study on animal safety and published reports of clinical experience in using dexpanthenol for various dermatoses (Refs. 2 and 3). In a 14-day animal safety study (Ref. 6), three preparations containing 2 percent dexpanthenol were orally administered to groups of six rats at a dose level of 50 milliliters/kilogram (mL/kg); no toxic effects were noted during observations for body weight and mortality. No information was provided about the treatment of the control group. Three of the reports of clinical experience (Refs. 7 through 10) included data on the use of dexpanthenol for the treatment of diaper rash. Kline (Ref. 7) summarized 12 years of clinical experience with a dexpanthenol cream and included an analysis of 500 case reports of dermatologic patients (28 were cases of diaper rash) to show that a wide variety of skin conditions were amenable to therapy with generally satisfactory results. Of the 28 cases of diaper dermatitis, satisfactory results were reported in 23 cases and unsatisfactory results in 5 cases. However, no other information is provided. Referring to a study by Litchfield (Ref. 8), Kline noted that Litchfield did not find any sensitization or rebound when 66 infants and children with various pediatric skin problems, including diaper rash, were treated with a combination product containing dexpanthenol and hydrocortisone. Kline and Caldwell (Ref. 9) treated 31 patients with various types of skin conditions, including 1 case of diaper rash, with either a 2 percent or 5 percent dexpanthenol cream and concluded that a concentration of 2 percent was just as effective as a concentration of 5 percent. No evidence of sensitization or other adverse effects were observed in these patients, some of whom were treated for over 1 year. Dubow (Ref. 10) described the treatment of diaper rash using dexpanthenol cream for relief of inflammation, in conjunction with other treatments, i.e., drying the diaper area and eliminating ammonia in contact with the skin. None of these authors provided detailed information on the procedures used, controls, or severity of the infants' diaper rash. These reports provide some limited evidence of the safety and effectiveness of dexpanthenol, but the data are inadequate to establish general recognition of the safety or effectiveness of dexpanthenol in the treatment of diaper rash.

Accordingly, the agency concludes that there are insufficient data available to classify dexpanthenol as safe or effective for the treatment or prevention of diaper rash and classifies the ingredient as Category III.

References

(1) OTC Volume 160067.
(2) OTC Volume 160104.
(3) OTC Volume 160204.
(4) Letter from S. Most, Block Drug Company, Inc., to L. Geismar, FDA, November 6, 1986, in OTC Volume 06DRSTFM, Docket No. 78N–021D, Dockets Management Branch.
(5) Letter from A. Ryan, Armour Pharmaceutical Co., to L. Geismar, FDA, January 7, 1987, in OTC Volume 06DRSTFM, Docket No. 78N–021D, Dockets Management Branch.
(6) "Acute Toxicity of Panthoderm®Cream, pantho-F® 1% and Panthoderm®Lotion," Project 0115, 1974, unpublished study, in OTC Volume 160104.
(7) Kline, P. R., "12 Years' Experience Using Pantothenylol Topically," Western Medicine, 4:78–80 and 100, 1963.
(8) Litchfield, H. R., "Treatment of Intertriginous Eruptions (Diaper Rash) and Infantile Eczemas," New York State Journal of Medicine, 60:3252–3257, 1960.
(9) Kline, P. R., and A. Caldwell, "Treatment of Various Dermatoses with Topical Application of Panthenol," New York State Journal of Medicine, 52:1141–1143, 1952.
(10) Dubow, E., "Ammoniacal Napkin Dermatitis in Infants," Archives of Pediatrics, 71:323–326, 1954.

M. Comments on Dimethicone

20. Two comments noted that silicone was identified on the agency's list of 50 ingredients in the advance notice of proposed rulemaking for OTC diaper rash drug products (47 FR 39439) but that it was not referred to any specific rulemaking. The comments recommended that silicone (dimethicone) be included in the skin protectant rulemaking and be classified as Category I for the treatment and prevention of diaper rash because this ingredient is generally recognized and commonly used for its properties of barrier-like action (especially to irritants which cause common diaper rash), water insolubility, and emollience.

The comments are correct that silicone, which is on the list of ingredients submitted to the Miscellaneous External Panel, was not referred to any of the four specific rulemakings in which OTC diaper rash drug products are being evaluated. Silicone is a general term, but it is often used to describe dimethicone (Refs. 1 and 2). Dimethicone is the preferred nomenclature because it identifies a defined compound that is official in The National Formulary (Ref. 3). Because there are various silicone compounds (Ref. 4), the agency is not classifying silicone per se, but is considering the only silicone ingredient for which data have been submitted, i.e., dimethicone.

The Topical Analgesic Panel recommended that 1 to 30 percent dimethicone, a water-repellent silicone oil (Ref. 4), be placed in Category I as a skin protectant for use on infants, children, and adults (43 FR 34628 at 34637). The agency concurred with the Panel's recommendations on dimethicone in the tentative final monograph for OTC skin protectant drug products (48 FR 6820 at 6832). Based on the recommendations of the Topical Analgesic Panel, the agency is classifying dimethicone, 1 to 30 percent, as Category I for the treatment or prevention of diaper rash. (See comment 8 above.)

References

(1) Marler, E.E.J., "Pharmacological and Chemical Synonyms," "Excerpta Medica," 7th Ed., Amsterdam, 1983, s. v. "dimeticone," "dimethicone," "silicone," and "simethicone."

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N. Comments on Lanolin

21. Two comments recommended Category I status for lanolin as a skin protectant for the treatment and prevention of diaper rash, stating that this ingredient is safe and acts as an effective barrier to irritants that cause common diaper rash. A third comment requested that lanolin be categorized as an active ingredient in the skin protectant rulemaking for use as a single ingredient or in combination, as permitted by the monograph, with an indication for the prevention of diaper rash. In support of the safety and effectiveness of lanolin as a skin protectant, the latter comment cited data submitted to the Miscellaneous External Panel (Ref. 1). The comment stated that animal and human test data included in the submission demonstrate lanolin's low order of irritation and sensitization, and that other data show that lanolin meets the definition of a skin protectant (an agent that protects injured or exposed skin or mucous membranes from harmful or annoying stimuli). The comment also based its request for a diaper rash prevention indication on the Topical Analgesic Panel's affirmation of this use for petrolatum (43 FR 34628 at 34639) and the Hemorrhoidal Panel's Category I classification of lanolin and petrolatum as protectants (45 FR 35578 at 35632 and 35634). To confirm the ability of these agents to protect the diaper area, the comment cited the Hemorrhoidal Panel's statement that "the barrier effect is supported by data indicating that infants' perianal skin is afforded significant protection against diaper wetness by application of a continuous film of petrolatum applied to the skin in the diaper area," (45 FR 35627). The comment also referred to an evaluation of moisturizers performed by Kligman, Grove, and Studemayer (Ref. 2) in which petrolatum and lanolin were determined to be the best moisturizers. Finally, the comment contended that the Ophthalmic panel's Category I classification of lanolin for treating conditions involving ocular membranes (an area more sensitive than the epidermis) (45 FR 30002 at 30044) further supports the safe and effective use of lanolin as a skin protectant for diaper rash.

Although lanolin is widely marketed and contained in many diaper rash products (Ref. 3), as well as other topical drug products, it has not been classified in the rulemaking for OTC skin protectant drug products. Lanolin was listed as one of the ingredients in marketed products submitted to the Miscellaneous External Panel in its statement on OTC drug products for the treatment of diaper rash (47 FR 39436 at 39439). In addition, as the comment noted, the Ophthalmic Panel classified lanolin as Category I as an ophthalmic emollient but did not establish a concentration range (45 FR 30002 at 30048). The Hemorrhodial Panel also classified lanolin Category I as a protectant at a concentration of at least 50 percent per dosage unit (45 FR 35576 at 35673). The agency concurred with these classifications in the tentative final and final monographs for OTC ophthalmic drug products (48 FR 29788 at 29798 and 53 FR 7076 at 7089) and in the tentative final monograph for OTC anorectal drug products (53 FR 30756 at 30782). In the final monograph for OTC ophthalmic drug products, the agency specified the concentration range for lanolin and anhydrous lanolin, as an emollient, to be 1 to 10 percent in combination with one or more oleaginous emollients included in the monograph (53 FR 7089).

The agency has reviewed the data submitted on lanolin and agrees that it qualifies as a skin protectant active ingredient for the treatment and prevention of diaper rash. Lanolin has a low sensitization potential and acts as an effective barrier to irritants that cause common diaper rash. Safety data on lanolin included in the submission (Ref. 1) consisted of reports of controlled animal and human studies and pertinent medical and scientific literature. The topical irritation potential of lanolin was determined by two primary irritation studies on rabbits: the Draize procedure demonstrated that lanolin was not a primary irritant, and the other study found lanolin to be slightly irritating at a 20-percent concentration in oil and nonirritating at a 10-percent concentration. There were no toxic symptoms or deaths when a 25-percent solution of lanolin in corn oil was given orally to mice. The acute oral LD^{50} (dose lethal to 50 percent of test animals) by gastric intubation in rats was estimated to be greater than 5 grams per kilogram. A 24-hour patch test on 10 humans with 10 percent lanolin in corn oil proved to be nontoxic and nonirritating.

The major safety consideration relates to the allergenicity of lanolin, and this is discussed by the Hemorrhoidal Panel in its advance notice of proposed rulemaking for OTC anorectal drug products. (See 45 FR 35632; May 27, 1980.) That Panel indicated that the data show that the incidence of lanolin allergy is extremely low. The agency is aware of other reports that further support the low incidence of lanolin

allergy. Weston and Weston (Ref. 4) report that lanolin has been thought to be a cause of contact allergy in children, but only two instances have been recorded in the literature. According to Weston and Weston, children who frequently apply lanolin to their skin for conditions such as atopic dermatitis or psoriasis do not develop an allergy to lanolin despite the long-term exposure. Kligman (Ref. 5) concluded that lanolin is an extremely weak sensitizer and its reputation as an allergen has been vastly inflated. Although lanolin may cause allergic reactions in sensitive individuals, the agency agrees with the Hemorrhoidal Panel (45 FR 35576 at 35632) and tentatively concludes that this ingredient can be used safely by the major part of the OTC target population and that no special warnings are needed. Further, the labeling of lanolin as an ingredient in the product should serve to alert sensitive individuals to its presence in the product.

The effectiveness data provided in the submission (Ref. 1) consist of pertinent medical and scientific literature that substantiates the activity of lanolin as a protectant and emollient. Although the literature does not contain controlled studies specific for diaper rash, it shows that the activity of lanolin is based on emollience, lubrication, and occlusiveness. These physical properties along with the findings of the Hemorrhoidal and Ophthalmic Panels are considered sufficient to support effectiveness for preventing and treating diaper rash. Although considered a safe and effective skin protectant for use in diaper rash drug products, none of the data include the concentration used for lanolin as an active ingredient in the various diaper rash products.

The agency has surveyed the marketplace (Refs. 3, 6, and 7) and found that lanolin is widely used as an ingredient in OTC diaper rash products. Products containing lanolin are currently being marketed with diaper rash claims such as "helps protect against urine and other irritants," and "provides a physical barrier" (Ref. 6). The Handbook of Nonprescription Drugs (Ref. 3) identifies 15 products that contain lanolin. Lanolin is often described as a base or vehicle (Refs. 3 and 6). It appears that lanolin is being marketed in diaper rash drug products only in combination with other ingredients, such as petrolatum and zinc oxide. Further, in the various submissions and in the Handbook of Nonprescription Drugs (Ref. 3), the concentration of lanolin (15.5 percent) is listed for only one product. Based on the primary irritation studies conducted on rabbits (Ref. 1), which showed lanolin to be slightly irritating at a 20-percent concentration and nonirritating at a 10-percent concentration, the agency does not believe that lanolin in diaper rash drug products should exceed 15.5 percent. Therefore, in this tentative final monograph, the agency is proposing a concentration of 15.5 percent lanolin, based on the only information available. The agency will consider revising this concentration if other supportive data are submitted.

Further, based on the agency's market survey, which showed that lanolin is used only in combination with other diaper rash ingredients, and the agency's actions in the rulemakings for OTC anorectal and ophthalmic drug products (see above), the agency is proposing that lanolin in diaper rash drug products may be used only in combination with certain other skin protectant active ingredients within the concentrations specified in proposed § 347.10. The agency invites comments and supporting data on the appropriateness of this and other concentrations of lanolin as an active ingredient in drug products labeled for the prevention and treatment of diaper rash and on this proposal to limit use of this ingredient to combination skin protectant diaper rash drug products.

References

(1) OTC Volume 160179.
(2) Kligman, A.M., G.L. Grove, and T.J. Studemayer, "Some Aspects of Dry Skin and its Treatment," in "Safety and Efficacy of Topical Drugs and Cosmetics," edited by A.M. Kligman and J.J. Leyden, Grune & Stratton, New York, p. 235, 1982.
(3) Smith, G.H., "Diaper Rash and Prickly Heat Products," in "Handbook of Nonprescription Drugs," 8th Ed., American Pharmaceutical Association, Washington, pp. 651–653, 1986.
(4) Weston, W.L., and J.A. Weston, "Allergic Contact Dermatitis in Children," American Journal of Diseases in Children, 138:932–936, 1984.
(5) Kligman, A.M., "Lanolin Allergy: Crisis or Comedy," Contact Dermatitis, 9:99–107, 1983.
(6) Huff, B. B., editor, "Physicians' Desk Reference For Nonprescription Drugs," 10th Ed., Medical Economics Co., Inc., Oradell, NJ. pp. 552, 573, and 682, 1989.
(7) Kastrup, E. K., editor, "Topical Diaper Rash Products," in "Facts and Comparisons," J. B. Lippincott Co., St. Louis, p. 563, August 1987.

O. Comment on Live Yeast Cell Derivative

22. In response to the advance notice of proposed rulemaking for OTC skin protectant drug products (43 FR 34628), the agency received a comment requesting removal of the Topical Analgesic Panel's limitation against the use of shark liver oil and live yeast cell derivative on children under 2 years of age without consulting a physician (Ref. 1). The comment argued that the Panel gave no reason for limiting the use of these ingredients and stated that both ingredients are safe and effective as skin protectants for the treatment of diaper rash for that age group. The comment also stated that the Panel failed to mention that a product containing both shark liver oil and live yeast cell derivative was submitted specifically for diaper rash (Ref. 2).

In its response in the tentative final monograph for OTC skin protectant drug products (see 48 FR 6820 at 6825, comment 12), the agency noted that the product referred to by the comment was listed at 43 FR 34629 as one of the marketed products submitted to the Topical Analgesic Panel. However, that Panel discussed the use of shark liver oil and live yeast cell derivative for use as skin protectants only. The agency deferred 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 pending completion of the agency's evaluation of diaper rash drug products.

The agency has reviewed the data contained in the submission (Ref. 2) and other available data and concludes that the data are insufficient to support the safe and effective use of live yeast cell derivative for the treatment of diaper rash on children under 2 years of age.

The submission included data to support the safe and effective use of live yeast cell derivative as a wound healing agent based on the ingredient's ability to increase oxygen utilization of dermal tissue, increase collagen formation of tissue, and increase the rate of healing of controlled wounds. The manufacturer stated that diaper rash is a tissue injury (wound) caused chemically (by urine, sweat, or humidity), mechanically (by friction or abrasion), or by inflammation and, consequently, a preparation used for the repair of such tissue injury should primarily possess wound healing properties. The agency's evaluation of the data related to use as a wound healing agent appears in the **Federal Register** of February 15, 1983 (48 FR 6820 at 6823). The agency concluded that there was insufficient evidence of the effectiveness of live yeast cell derivative as a wound healing aid. The majority of the clinical data submitted have concerned wounds, which represent a break in the continuity of the skin in which the wound healing properties of live yeast cell derivative mentioned by

the submission would be beneficial. However, the agency believes that diaper rash amenable to treatment with an OTC drug product does not represent a break in the continuity of the skin comparable to the wounds studied, and the data do not establish that the stated wound healing properties of live yeast cell derivative are significant factors in the healing of diaper rash. The agency's discussion in the **Federal Register** of February 15, 1983 did not involve the use of live yeast cell derivative in infants. However, the agency notes that the Topical Analgesic Panel, while finding live yeast cell derivative safe, limited its use to adults and children 2 years of age and older. The Panel stated that there is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician (43 FR 34628 at 34646).

The submission (Ref. 2) also contains a brief summary of a diaper rash study conducted by Minsky. The study compared an ointment containing 2,000 units of live yeast cell derivative and 3 percent shark liver oil to an undescribed placebo on 54 newborns with peri-rectal diaper rash. All cases had erythema plus either vesiculation, papulation, or excoriation. The infants were divided into a test group of 29 infants treated with the live yeast cell derivative/shark liver oil combination and a control group of 25 infants treated with the placebo. In the test group 86 percent of the infants were cured or improved as opposed to 76 percent in the control group. No adverse reactions to either treatment were noted. It was noted that the test ointment was of a thick consistency that adhered to the affected area. Although the study demonstrates some benefit of the test ointment over the placebo because of the nature of the test ointment and the fact that it contained both shark liver oil and live yeast cell derivative, no conclusions can be made as to the effectiveness of live yeast cell derivative as a single ingredient. The lack of any adverse reactions in the 29 infants in the test group is not considered sufficient data to generally recognize this ingredient as being safe for the treatment of diaper rash in children under 2 years of age. Therefore, the agency places live yeast cell derivative in Category III for safety and effectiveness for its use in the treatment of diaper rash.

The agency's evaluation of shark liver oil appears in comment 8 above.

References

(1) Comment No. C00006, Docket No. 78N–0021, Dockets Management Branch.
(2) OTC Volume 060113.

P. Comment on Microporous Cellulose

23. A submission to the Miscellaneous External Panel contained data on a product containing 45 percent microporous cellulose labeled to help prevent diaper rash (Ref. 1). The submission included patents for the individual components of microporous cellulose, i.e., microporous alpha cellulose and corn cob derivative. The manufacturer attributed the extraordinary ability of the product to absorb moisture to the microporous alpha cellulose and corn cob derivative content. Although the submission was reviewed by the Panel in preparing its statement on diaper rash drug products, the Panel made no recommendations concerning the individual ingredients.

The agency has reviewed the submission and concludes that the data are insufficient to support the safety and effectiveness of microporous cellulose used for the prevention of diaper rash. The patents included in the submission Provided information on the physical and chemical nature of the components of microporous cellulose, but did not provide any data on the use of this ingredient for diaper rash.

The submission described a patch test conducted on 100 white females using the product. A one-half inch square of clean white blotting paper was impregnated with the product and applied to a previously cleaned site on the subjects' backs and allowed to remain in place for 48 hours. Observations of the site were made immediately after removal of the patch, again after 15 minutes, and again after 24 hours. There was no evidence of any irritation, and the investigator concluded that the product is not a primary irritant. While the agency believes that the patch test is illustrative of the low dermal irritancy of the product, the test did not address the safety of using microporous cellulose on infants' skin under the conditions such as those present in the diaper area, *e.g.*, moisture and friction between opposing skin surfaces. In addition, the ages of the subjects were not provided; therefore, no conclusions on the effect of the product on infant skin can be made.

An in vitro study comparing the absorptive capacities of various marketed powder products was also included in the submission. This study showed a superior moisture absorbing capacity for the submitted product. However, the agency does not consider this study as presenting sufficient effectiveness data to support the use of microporous cellulose to help prevent diaper rash.

Based on the above, the agency is classifying microporous cellulose in Category III for safety and effectiveness for the prevention of diaper rash.

Reference

(1) OTC Volume 160357.

Q. Comments on Mineral Oil.

24. Two comments requested Category I status for mineral oil as a skin protectant for the treatment and prevention of diaper rash. Both comments contended that mineral oil has recognized properties of barrier-like action, water insolubility, and emollience plus a long record of safe and effective use, particularly on infants' skin.

Submissions (Refs. 1, 2, and 3) to the rulemaking for OTC skin protectant drug products included safety data for mineral oil and efficacy data for its use as a skin emollient/lubricant. Diaper rash was included among the labeled uses. The safety data included acute oral toxicity in mice, acute dermal toxicity in rabbits, dermal irritation in rabbits, and occular irritation in rabbits. The LD_{50} was shown to be greater than 20 mL/kg. Mineral oil was not shown to be a primary irritant on the skin, and it caused virtually no eye irritation. The efficacy data for mineral oil consisted of information to show its properties of occlusion, emollience, protection, lubrication, and as a moisturizer. However, none of the data included use on patients with diaper rash.

Mineral oil has been evaluated in two OTC drug rulemakings. In the **Federal Register** of May 27, 1980, the Hemorrhoidal Panel classified mineral oil in Category I as a protectant for anorectal use in concentrations of at least 50 percent (45 FR 35576 at 35633). In its report, the Panel stated that

> * * * mineral oil is effective as a U protectant. A layer of mineral oil is less effective than petrolatum in reducing moisture loss from the outer layer of the skin of the forearm, but it is significantly greater than other materials tested * * *. This property is also interpreted by the Panel to provide occlusion of the area from external exposure to air, liquids, or other substances within reasonable limits.

The Ophthalmic Panel classified mineral oil in Category I as an ophthalmic emollient (45 FR 30002; May 6, 1980). The agency agreed with this classification in the tentative final (48 FR 29788; June 28, 1983) and final (53 FR 7076; March 4, 1988) monographs for OTC ophthalmic drug products.

Upon surveying the marketplace (Refs. 4 and 5), the agency notes that mineral oil is used as an ingredient in

OTC diaper rash products. In some products, mineral oil is not labeled as an active ingredient and in other products, such as baby oils containing a diaper rash claim, it appears to be an active ingredient, at up to a 100 percent concentration.

The Hemorrhoidal Panel commented that mineral hydrocarbons are not subject to metabolism and can thus remain on the skin indefinitely unless physically removed. The Panel noted that these mineral fats remain on the skin and can produce chronic irritation fibrosis and foliculitis (45 FR 35576 at 35633). The Panel noted a potential problem with repeated application of mineral oil hydrocarbons to fissured anal areas or to raw mucosa, but recommended that mineral oil was safe for use in anorectal products. The Panel further recommended that mineral oil be used in a concentration of at least 50 percent per dosage unit and that use not exceed six applications per 24 hours or after each bowel movement. The agency proposed this usage in the tentative final monograph for OTC anorectal drug products (53 FR 30756 at 30782 and 30784).

The Panel made the following statement about mineral oil at 45 FR 35633:

> Because it is not absorbed, its effect may be prolonged for hours until it is physically removed. The effectiveness of mineral oil and analogous petroleum-derived agents such as lubricants, protective agents, and stable vehicles must be weighed against potential accumulation and persistence until physically removed.

The agency is proposing directions for all diaper rash drug products that include "cleanse the diaper area, and allow to dry." The agency believes that any potential accumulation will be minimized if these directions are followed, and thus there is no need to limit the number of daily applications of a diaper rash drug product containing mineral oil.

The effectiveness data provided in the submission (Ref. 3) consist of pertinent medical and scientific literature that substantiates the activity of mineral oil as a protectant and emollient. Although the literature does not contain controlled studies specific for diaper rash, it shows that the activity of mineral oil is based on emollience, lubrication, and occlusion. These physical properties along with the findings of the Hemorrhoidal and Ophthalmic Panels are considered sufficient to support effectiveness for including mineral oil in the monograph for the prevention and treatment of diaper rash. The agency believes that mineral oil can be safely and effectively used as a single ingredient at up to a 100 percent concentration. The lower concentration is being proposed as 50 percent in accord with the anorectal tentative final monograph. Mineral oil may be combined with other skin protectant active ingredients listed in § 347.10 provided each ingredient in the combination is within the concentrations specified in § 347.10.

References

(1) OTC Volume 160052.
(2) OTC Volume 160086.
(3) Comment No. C00018, Docket No. 78N–0021, Dockets Management Branch.
(4) Sadik, F., "Diaper Rash and Prickly Heat," in "Handbook of Non-Prescription Drugs," 1973 Ed., by G.B. Griffenhagen and L.L. Hawkins, American Pharmaceutical Association, Washington, pp. 184–189, 1973.
(5) Kastrup, E.K., editor, "Topical Diaper Rash Products," in "Facts and Comparisons," J.B. Lippincott Co., St. Louis, p. 563, August 1987.

R. Comment on Peru Balsam Oil

25. One manufacturer submitted data (Refs. 1, 2, and 3) to the Miscellaneous External Panel for a combination product that included Peru balsam oil at a concentration of 1.5 percent as an active ingredient, with several labeling claims, one of which was the treatment and prevention of diaper rash. The submissions included tests performed on human newborn infants (Ref. 1), toxicity data, and monographs on Peru balsam oil published by the Research Institute for Fragrance Materials (Ref. 3). Subsequently, the manufacturer informed the agency that the Peru balsam oil in its diaper rash drug products is used as a fragrance at the following concentrations: ointment, 1.5 percent; powder, 0.125 percent; and lotion, 0.32 percent (Refs. 4 and 5).

Balsam Peru and balsam Peru oil were included in the list of ingredients in marketed diaper rash drug products submitted to the Miscellaneous External Panel (47 FR 39436 at 39439), but the Panel did not review or classify individual ingredients. Peruvian balsam was reviewed by the Hemorrhoidal Panel as a topical wound-healing agent (45 FR 35576 at 35654). That Panel concluded that Peruvian balsam was safe in concentrations up to 3 percent, but effectiveness in relieving anorectal symptoms such as burning, pain, itch, or swelling, or as a wound healing agent, had not been demonstrated. The Panel recommended Category III status for use in anorectal drug products.

The agency has evaluated the submissions and notes, as stated in one submission (Ref. 3), that the ingredient in the diaper rash products is not Peru balsam (which was evaluated by the Hemorrhoidal Panel), but is Peru balsam oil, a purified Peru balsam prepared by extraction with volatile solvents or distillation from balsam of Peru (Ref. 6).

The safety data in the submissions include a patch test performed on 200 infants with a cream product containing Peru balsam oil (Ref. 1). However, the concentration of Peru balsam oil in the cream product was not provided. The patch test showed no evidence of primary irritation or allergenicity. Fifty of the infants were re-tested and no secondary allergenicity was observed.

An acute dermal toxicity study involved a single 24-hour application of Peru balsam oil (2 g/kg) to the clipped, abraded, abdominal skin of 10 rabbits, (Ref. 3). No evidence of toxicity from percutaneous absorption and no abnormalities at necropsy were observed. A single-dose (5 g/kg) oral toxicity study was conducted on 10 albino male rats. The rats were observed on the day of the test and daily for 14 days (Ref. 3). Ten deaths occurred 3 to 24 hours after dosing; lethargy, catalepsy, loss of righting reflex, and slow respiration preceded the deaths.

To evaluate Peru balsam oil for systemic toxicity, an acute dermal toxicity study was conducted on 12 albino rabbits (Ref. 3). The test material was applied to the clipped, intact, and abraded skin areas (backs of the animals) and the area was covered with a snug-fitting rubber sleeve for 24 hours. The animals were divided into three groups of four animals each, and dose levels of 2.0 mL, 3.9 mL and 6.0 mL per kg of body weight were used. After the 24-hours exposure, the sleeves were removed, and the skin reactions were recorded. The animals were wiped down and observed for 14 days. There was no erythema or edema at the end of the 24-hours contact and during the 14 days of observation. No toxic effects and no significant changes in hematogram values were observed. Maximization tests were done on 25 healthy males to determine the contact-sensitizing potential of Peru balsam oil (Ref. 3). The Peru balsam oil was applied under occlusion to the same sites on the volar forearms for five alternate-day 48-hour periods, after pre-treatment for 24 hours with 5 percent aqueous sodium lauryl sulfate under occlusion. After a 10-day rest period, a challenge patch was applied under occlusion to fresh sites for 48 hours, preceded by a 1-hour application of 10 percent aqueous lauryl sulfate under occlusion. No contact-sensitization occurred in any of the individuals tested. Although the concentration of the Peru balsam oil used in these tests was not stated, the studies indicate that it is

unlikely that Peru balsam oil at the concentration tested would present a danger of contact-sensitization in normal, intended use. Other information included in the Monographs on Fragrance Raw Materials (Ref. 6) indicates that Peru balsam and Peru balsam oil would be safe in the low concentrations present in these diaper rash drug products.

One clinical evaluation was included in the submission (Ref. 1) to support the effectiveness of Peru balsam oil for diaper rash use. During a 2-year span, a cream product was tested on 558 newborn infants with perianal and/or diaper dermatitis. The average stay of the infants in the hospital and treatment time was 5 days. The dermatitis cleared in 537 of the infants. However, the submission did not provide any information on the severity of the rashes, the frequency of application of the cream, or whether the 21 infants who did not respond became worse. There was no mention whether the study was controlled, i.e., whether there was an infant control group or a vehicle control. Further, the concentration of Peru balsam oil in the product was not stated. Therefore, this study is not sufficient to support the effectiveness of Peru balsam oil for the treatment and/or prevention of diaper rash.

Based on current information, Peru balsam oil is labeled as an inactive ingredient in the manufacturer's products as a fragrance at a 0.125-, 0.32-, and 1.5-percent concentration (Refs. 4 and 5). Based upon the Monographs on Fragrance Raw Materials (Ref. 6), the agency finds 0.125 and 0.32 percent concentrations of Peru balsam oil acceptable as a fragrance. However, the agency has concerns as to whether the 1.5 percent concentration in the ointment product has any active ingredient properties. The agency notes that the United States Dispensatory (Ref. 7) indicates that Peruvian balsam (Peru balsam) has a number of drug uses when applied topically in the form of an ointment or alcoholic solution. Peruvian balsam was once official in The National Formulary (Ref. 8). In addition, Peruvian balsam is currently marketed as an active ingredient in a 1.26- and a 1.8-percent concentration in topical anorectal drug products (Ref. 9). Further, testimonials from several physicians (Ref. 1) attribute superiority of the manufacturer's diaper rash product over other products to the Peru balsam contained in it. Based on the above and the description of Peru balsam oil as a purified form of Peru balsam (Ref. 6), the agency questions the inactive ingredient status of a 1.5-percent concentration of Peru balsam oil used as a fragrance in a diaper rash drug product. As a rule, an inactive ingredient should be used only at a level required to achieve its intended function in the product. The concentration in the manufacturer's ointment product is almost 5 times that used in its lotion product and is 12 times that used in its powder product (Ref. 4). The agency needs additional supportive evidence that a 1.5-percent concentration of Peru balsam oil does not have any active ingredient properties when used in a diaper rash drug product. Based on the information available at this time, the agency classifies Peru balsam and Peru balsam oil at concentrations up to 3 percent in Category III for use in OTC diaper rash drug products.

References

(1) OTC Volume 160041.
(2) OTC Volume 160088.
(3) OTC Volume 160421.
(4) Letter from E. Waxman, Macsil, Inc., to W. E. Gilbertson, FDA, February 5, 1983, LET00020, Docket No. 78N-0021, Dockets Management Branch.
(5) Current labeling for Balmex Ointment in OTC Volume 06DRSTFM, Docket No. 78N-021D, Dockets Management Branch.
(6) Opdyke, D.L.J., editor, "Monographs on Fragrance Raw Materials," Research Institute for Fragrance Materials, Inc., in OTC Volume 160421.
(7) Osol, A., and R. Pratt, editors, "Peruvian Balsam," in "The Dispensatory of the United States of America," 27th Ed., J.B. Lippincott Co., Philadelphia, p. 888, 1973.
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S. Comments on Sodium Bicarbonate

26. One comment stated that it had submitted information on the safety and efficacy of baking soda (sodium bicarbonate) used as an external analgesic and as a skin protectant. Referring to FDA's decision, published in the tentative final monograph for OTC skin protectant drug products (48 FR at 6830; February 15, 1983), that transferred sodium bicarbonate from the rulemaking for OTC skin protectant drug products to the rulemaking for OTC external analgesic drug products, the comment stated the baking soda should be considered in both rulemakings.

At the time that the tentative final monograph for OTC skin protectant drug products was published, the agency had determined that, based on the claims for sodium bicarbonate currently in that rulemaking, the uses for sodium bicarbonate under consideration would be addressed more appropriately in the rulemaking for OTC external analgesic drug products. Now that the agency has reviewed the information on the use of sodium bicarbonate for the treatment and prevention of diaper rash, the agency has determined that the diaper rash uses of sodium bicarbonate should be included in the skin protectant rulemaking. Accordingly, as the comment requested, sodium bicarbonate is now being considered in both rulemakings. (See also comment 27 below.)

27. One comment requested that sodium bicarbonate be classified in Category I for the treatment of diaper rash. The comment asked that data on sodium bicarbonate previously submitted to the Miscellaneous External Panel (Ref. 1) and to the rulemaking for OTC skin protectant drug products (Refs. 2 and 3) be considered along with the supplementary information submitted (Refs. 4 and 5) to demonstrate that sodium bicarbonate has been used and marketed for many dermatological conditions including diaper rash. The comment included a "dermatological summary of baking soda" (sodium bicarbonate) (Ref. 6) which contained references in the medical literature on the topical use of sodium bicarbonate (e. g., as a powder and in a bath) in a number of dermatological conditions.

The comment noted that, although sodium bicarbonate has not been the subject of double-blind clinical trials (a concept of relatively recent development, circa 1952), it has been used for a long time for its effectiveness in the treatment of a variety of skin conditions (Ref. 6). It is recommended by physicians and cited in medical literature. The basis of its efficacy is not completely understood. One mechanism of action to explain the topical effect of sodium bicarbonate is that it, as well as other mild alkali, softens the epithelial surface, skin, or mucous membranes resulting in a reduction of irritation when the skin is subject to a variety of irritants (Refs. 6 and 7). Urine and feces are irritating to the skin of infants when they are kept in close contact with the skin by diapers.

The Topical Analgesic Panel reviewed and classified sodium bicarbonate as safe and effective for use as a skin protectant (43 FR 34640). That Panel concluded that sodium bicarbonate is safe for use as a skin protectant with no age or concentration limits. However, that Panel did not review sodium bicarbonate for any diaper rash uses, and diaper rash was not included in the tentative final monograph for OTC skin protectant drug products (48 FR 6820; February 15, 1983). In addition, the

agency did not include sodium bicarbonate in the tentative final monograph for OTC skin protectant drug products because the indications submitted up to that time for products containing sodium bicarbonate were very similar to indications being evaluated for OTC external analgesic drug products (e.g., for the temporary relief of pain and itching due to minor burns, sunburn, * * * insect bites, and minor skin irritations"). Accordingly, sodium bicarbonate was transferred to the rulemaking for OTC external analgesic drug products. (See comment 33 at 48 FR 6830.)

The agency has reviewed the comments as well as other information available on sodium bicarbonate and is aware of one report of an adverse reaction in a 4-month-old infant after treatment of diaper rash with sodium bicarbonate (Ref. 8). The adverse reaction report states that liberal amounts of sodium bicarbonate and petrolatum had been applied to a severe diaper rash at every diaper change for more than a week. Physical examination showed a diffuse erythematous rash with large areas of denuded skin extending over most of the diaper area. The infant experienced hypokalemic metabolic alkalosis which the authors attributed to excessive sodium bicarbonate absorption from the baking soda that was applied to the diaper rash. The infant recovered completely following discontinuation of sodium bicarbonate treatments.

In the absence of supportive data, the agency is concerned about repetitive application of sodium bicarbonate powder to the diaper area for a prolonged period of time. The agency acknowledges that the Topical Analgesic Panel concluded that a 1-to-100 percent sodium bicarbonate preparation was safe for topical use on infants (43 FR 34628 at 34640). However, in evaluating the uses described by the Panel, the agency notes that the Panel was primarily considering limited application for short-term relief, *e.g.*, use in a bath or in the form of a moist paste or a solution. Limited application such as use in an occasional bath appears to present much less of a safety problem than repetitive application to the diaper area of an infant.

The agency has reviewed the references submitted by the comment; they state that the most common method of use of sodium bicarbonate for rashes is in solution as a bath, not as a powder. Weinberg and Hoekelman (Ref. 9) prescribe application of aqueous solutions in the form of baths, soaks, or wet dressings for their anti-inflammatory and drying actions. The authors include sodium bicarbonate among the substances commonly added to make the solutions. A marketed product containing sodium bicarbonate provides directions for emollient baths to relieve skin irritations (Ref. 1). Regarding the use of sodium bicarbonate for such baths, the submission (Ref. 1) cites the Merck Manual (Ref. 10) as recommending that 8 ounces of sodium bicarbonate be dissolved in about 30 gallons of warm water and that the patient should remain in the bath for 10 to 30 minutes or longer. The skin should be patted dry rather than rubbed so that a thin film of the drug remains on the skin. Other submitted data (Ref. 6) indicated that although there is variation regarding the recommended or optial concentration of sodium bicarbonate for baths and solutions, a range of 1 to 5 percent would encompass most of the concentrations.

Although a sodium bicarbonate bath may be useful in alleviating mild cases of irritation resulting from diaper rash, the data submitted by the comment do not contain any information or studies specific for diaper rash. Information is needed to show that sodium bicarbonate acts to treat or prevent diaper rash. Softening and soothing the skin, the actions described by the comment for sodium bicarbonate baths, are cosmetic claims. Further, the agency is unaware of any sodium bicarbonate product labeled for diaper rash bearing complete indications, directions, and warnings. The agency believes the information submitted is not adequate to show the safety and effectiveness of sodium bicarbonate, used as a bath or as a powder, for the treatment or prevention of diaper rash. Accordingly, the agency is classifying sodium bicarbonate in Category III for safety and efficacy for diaper rash.

References

(1) OTC Volume 160032.
(2) Comment C00027, Docket No. 78N-0021, Dockets Management Branch.
(3) Comment C00050, Docket No. 78N-0021, Dockets Management Branch.
(4) Comment C00047, Docket No. 78N-0301, Dockets Management Branch.
(5) Comment C00065, Docket No. 78N-0301, Dockets Management Branch.
(6) Eisenstat, B. A., "Dermatological Summary of Baking Soda," unpublished study, pp. 1-7, October 7, 1983.
(7) Sollmann, T., "A Manual of Pharmacology and its Applications to Therapeutics and Toxicology," 7th Ed., W. B. Saunders Co., Philadelphia, p. 121, 1948.
(8) Gonzalez, J., and R. J. Hogg, "Metabolic Alkalosis Secondary to Baking Soda Treatment of a Diaper Rash," Pediatrics, 67:820-822, 1981.
(9) Weinberg, S., and R. A. Hoekelman, "Dermatology for the Primary Care Practitioner," McGraw-Hill, New York, p. 112, 1978.
(10) Lyght, C. E., editor, "The Merck Manual," 9th Ed., Merck and Co., Rahway, NJ, p. 1756, 1956.

T. Comments on Talc

28. Two comments requested Category I status for talc for the treatment and prevention of diaper rash. The comments noted that talc was among a number of ingredients contained in marketed products for diaper rash that had not been referred to any advance notice of proposed rulemaking. The comments stated that talc, which has a long record of safe and effective use on infants skin, should be referred to the skin protectant rulemaking because of its barrier like action, water insolubility, and emollience. The comments concluded that talc acts as an effective barrier to irritants that cause common diaper rash.

The agency agrees with the comments that talc should be considered for inclusion in the skin protectant rulemaking based on its physical properties. In the reopening of the administrative record for OTC skin protectant drug products, the Miscellaneous External Panel presented its conclusions and recommendations on OTC drug products containing skin protectant ingredients for the treatment and prevention of diaper rash. Talc was included in the list of ingredients in marketed products submitted to that Panel (47 FR 39436 at 39439). The Panel stated that most diaper rash treatments, e.g., talc and zinc oxide ointment and paste, help by protecting the skin, acting as a physical barrier to irritants, and absorbing or adsorbing moisture. The Panel discussed talc at its meetings on April 3, 1977 (Ref. 1) and June 5, 1977 (Ref. 2) and determined that talc was an adsorbent to be used on skin areas of excess moisture and as an aid in the prevention of skin chafing, diaper rash, and heat rash. The Panel decided that talc should be Category I for use on intact skin with the following labeling: "Indications: For use as an absorbent on skin areas of excess moisture and as an aid in prevention of skin chafing, diaper rash, and heat rash; Warning: Do not use on broken skin, rashes, or open wounds," (Refs. 2 and 3). At its forty-first meeting on October 5 and 6, 1980 (Ref. 4), the Panel reaffirmed its previous decision that talc should be classified Category I for safety and effectiveness for the prevention of diaper rash. Nevertheless, in its final

recommendations to the agency, the Panel did not classify any ingredients for use in diaper rash.

A standard text book reference submitted by one of the comments (Ref. 5) included talc among the powdered agents used in treating diaper rash. The text describes talc as a natural hydrous magnesium silicate that allays irritation, prevents chafing, and absorbs sweat; it is similar to ointments and creams in that it adheres well to the skin. Talc was also identified as an ingredient in many of the products marketed for diaper rash that were listed in the text.

At the 1951 Round Table Discussion of the American Academy of Pediatrics (Ref. 6), talc was approved in the routine care of the newborn because it does not plug the pores. One standard text (Ref. 7) stated that talc remains the most important constituent of baby powder because it has excellent slip characteristics, good adhesion to the skin, and acts as a lubricant where skin surfaces are in apposition, as in the diaper area (buttocks and groin), and because it is water repellent and prevents chafing. Other authors discuss the use of talc for the treatment (Refs. 5, 8, and 9) as well as for the prevention (Ref. 10) of diaper rash.

Based on an analysis of the above information and the long marketing history of talc in diaper rash drug products, the agency tentatively concludes that talc can be generally recognized as safe and effective for the prevention and treatment of diaper rash. Although the Panel recommended talc only for the prevention of diaper rash, the agency believes talc can be used for the treatment of diaper rash provided it contains the same warning, i.e., not to use on broken skin, as the Panel recommended for prevention of diaper rash (Ref. 3). This warning is necessary because crusting, infection (Ref. 5), and skin granulomas (Refs. 11 and 12) have been known to result when talc and other powders (Ref. 13) are applied to broken skin.

While recognizing extensive use of powdered dosage forms for many years, the agency believes that an additional warning for diaper rash drug products in a powdered dosage form is needed because of numerous reported incidences of accidental inhalation of baby powders appearing in the literature (Refs. 5, 11, 12, and 14 through 19). Smith (Ref. 5) states that powders should be used cautiously and parents should be instructed to apply these powder products carefully to prevent the infant from inhaling the powder which may be harmful and could lead to chemical pneumonia. One study (Ref. 14) showed that baby powder inhalation occurs more frequently in children under 5 years of age than previous literature indicates. An age analysis of 34 cases showed that 55 percent of the children were under 1 year of age, 41 percent were in their second year, and 4 percent were over 2 years of age. The study showed that 73 percent of the children were being changed at the time inhalation occurred, and that one child developed aspiration pneumonia. In a later talc-aspiration report (Ref. 17), another child required ventilation on a respirator for several days. Moss (Ref. 18) mentioned that 50 cases of talcum powder aspiration are reported annually to one poison control center, but a survey of 100 mothers of children under 2 years of age indicated that 42 percent were unaware of the dangers if a child inhaled the powder. It appears that these cases have not been reported to the agency.

Several case histories of adverse reactions after inhalation of talcum powder are described in the literature. The youngest child was a 1-month old infant who went into cardiorespiratory arrest after powder was poured into her mouth and nose by a 3-year old sibling (Ref. 15). The infant received resuscitation and survived. Molnar, Nathenson, and Edberg (Ref. 16) reported that a 22-month old boy died of intractable cardiopulmonary failure, caused by respiratory distress and perioral cyanosis, 20 hours after inhaling talcum powder while playing with a container of the substance. Hughes and Kalmer (Ref. 11) reported that a 14-month old child developed severe respiratory distress after inhaling talcum powder when playing with the container, but recovered after treatment. Another report (Ref. 19) described five cases of children between 1 and 2 years of age who inhaled talcum powder. Three of these children died, even though they had received the recommended treatment of humidified oxygen in a tent, antibiotics, and epinephrine. The two survivors received corticosteroid drugs in addition to the other treatment.

Although talc has been implicated in these toxic episodes when aspirated accidentally or through misuse, the agency believes that talc can be labeled appropriately for safe OTC use. Therefore, the agency is proposing the following warnings for products containing talc: (1) "Do not use on broken skin." (2) "Keep powder away from child's face to avoid inhalation, which can cause breathing problems." (See also comment 7 above for discussion of directions for powder products.)

Although the Panel recommended that talc be Category I for the prevention of diaper rash, it did not recommend a safe and effective concentration range. None of the submissions to the Panel contained data regarding the concentration of talc in diaper rash products, and the comments did not provide any information on this subject. The agency has surveyed the marketplace and determined that most standard text books do not indicate a concentration range for talc in marketed diaper rash drug products. Only one of seven products containing talc used for diaper rash listed in the "Handbook of Nonprescription Drugs" (Ref. 5) provides its concentration (45 percent talc).

The agency is aware that up to 100 percent talc is used in some cosmetic products, e.g., dusting powders, and that consumers may use such products for preventing or treating diaper rash. Data submitted to the Miscellaneous External Panel (Ref. 20) on cosmetic talc indicated that with normal use it is not hazardous to health. Cosmetic talc should contain at least 90 percent platy talc (having flat as opposed to fibrous particles) that is free of detectable amounts of fibrous minerals, including asbestos. Cosmetic talc is not an allergen and does not alter the viability or phagocytic activity of pulmonary macrophages. Exposure of hamsters to cosmetic talc dust containing approximately 8 mg per cubic meter of respirable particles for periods of up to 2 and 1/2 hours per day for 300 days failed to produce any significant pulmonary or other pathological changes or differences in morbidity or mortality. The hamsters were exposed to a dust dose of up to 1,850 times the median human exposure. An epidemiological study of cosmetic talc millers who began their employment between 1921 and 1950 showed no increased incidences of death due to respiratory disease. The millers' exposure to talc dust was 384 times larger each day than a consumer's daily exposure to cosmetic talc powders.

The agency believes that products containing these higher concentrations of talc can be safely used on infants provided they contain the warnings discussed above. Therefore, the agency is tentatively proposing the concentration range for talc for use in diaper rash drug products at 45 to 100 percent and is inviting comments and data on this proposed concentration range and the proposed warnings.

Accordingly, the agency is tentatively classifying talc (45 to 100 percent) in Category I for use in the treatment and prevention of diaper rash with labeling

that includes the two warnings discussed above.

References

(1) Transcript of Proceedings of the Advisory Review Panel on OTC Miscellaneous External Drug Products, April 3, 1977, pp. 20–43, in OTC Volume 06DRSTFM, Docket No. 78N–021D, Dockets Management Branch.

(2) Transcript of Proceedings of the Advisory Review Panel on OTC Miscellaneous External Drug Products, June 5, 1977, pp. 22–46, in OTC Volume 06DRSTFM, Docket No. 78N–021D, Dockets Management Branch.

(3) Summary Minutes of the Eighteenth Meeting of the Advisory Review Panel on OTC Miscellaneous External Drug Products, June 5 and 6, 1977, Docket No. 78N–0021, Dockets Management Branch.

(4) Summary Minutes of the Forty-first Meeting of the Advisory Review Panel on OTC Miscellaneous External Drug Products, October 5 and 6, 1980, Docket No. 78N–0021, Dockets Management Branch.

(5) Smith, G.H., "Diaper Rash and Prickly Heat Products," in "Handbook of Nonprescription Drugs," 7th Ed., American Pharmaceutical Association, Washington, pp. 605–614, 1982.

(6) Osborne, E.D., et al., "Round Table Discussion: Pediatric Dermatology," American Academy of Pediatrics, 10:710–720, 1952.

(7) Barnett, G., "Baby Toiletries," in "Cosmetics—Science and Technology," 2d Ed., Wiley-Interscience, New York pp. 136 and 152, 1972.

(8) Brown, M.S., "Over-the-Counter Drugs for Skin Disorders, Part 3: Aids for Heat and Diaper Rash," Nurse Practitioner, July-August: 28–30,36, and 41, 1977.

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(10) Williams, M.L.K., "How I Treat Diaper Rashes," Medical Times, 108:50–53, 1980.

(11) Hughes, W.T., and T. Kalmer, "Massive Talc Aspiration," American Journal of Diseases of Children. 111:653–654, 1966.

(12) Wade, A., editor, Martindale, "The Extra Pharmacopoeia," 27th Ed., The Pharmaceutical Press, London, p. 455, 1977.

(13) Kelly, R., and P.E. Campbell, "Granuloma Glutaeale Infantum with Starch Granules in the Lesion," The Medical Journal of Australia, 2:438–439, 1973.

(14) "The Hazards of Baby Powder," Medical Science Bulletin—2, 4:2, 1981.

(15) Brouillette, F., and M.L. Weber, "Massive Aspiration of Talcum Powder by an Infant," Canadian Medical Association Journal, 119:354–355, 1978.

(16) Molnar, J.J., G. Nathenson, and S. Edberg, "Fatal Aspiration of Talcum Powder by a Child," The New England Journal of Medicine, 266:36–37, 1962.

(17) Mofenson, H.C., et al, "Baby Powder—A Hazard!", Pediatrics, 68:265–266, 1981.

(18) Moss, M.H., "Dangers from Talcum Powder", letter to the editor, Pediatrics, 43:1058, 1969.

(19) "Accidental Inhalation of Talcum Powder," British Medical Journal, 4:5–6, 1969.

(20) OTC Volume 160191.

U. Comments on Vitamins A and D

29. Two comments requested Category I status for vitamins A and D as ingredients in the skin protectant rulemaking for diaper rash drug products. The comments did not submit any data to establish safety and effectiveness, but argued that vitamins A and D have recognized properties of barrier-like action, water insolubility, and emollience. The comments concluded that these ingredients have a long history of use on infant skin and should receive favorable consideration as safe and effective skin protectants for the treatment and prevention of diaper rash because they act as an effective barrier to irritants that cause common diaper rash.

Note: "Vitamin D" was the name designated for this ingredient by the Panel in its statement. "Cholecalciferol" is the official title in the current edition of "USAN and the USP dictionary of drug names" (Ref. 1), and will be used in this document.

Vitamin A and cholecalciferol have not been classified as skin protectants in any rulemaking in the OTC drug review. The Hemorrhoidal Panel evaluated these ingredients as wound-healing agents in OTC anorectal drug products and classified them in Category III (45 FR 35576 at 35655 and 35656). That Panel advised that vitamin A is safe topically at an adult dosage of 1,710 International Units (IU) (0.5 mg) per dosage unit, not to exceed 10,000 IU (3.44 mg) per 24 hours and that cholecalciferol is safe topically at an adult dosage of 4.5 IU (0.00011 mg) per unit dose, not to exceed 27 IU (0.00066 mg) per 24 hours. That Panel also reviewed cod liver oil (which contains vitamin A and cholecalciferol) for use as a skin protectant and wound-healing agent and advised that cod liver oil is safe topically at an adult dosage not to exceed 10,000 IU vitamin A and 400 IU cholecalciferol per 24 hours and classified it in Category I as a skin protectant (45 FR 35630) and Category III as a wound healing agent (45 FR 35650). The Panel stated that the protectant effect of cod liver oil is attributed to the bland and soothing effect associated with its oily nature (45 FR 35630) and that no definitive clinical data support the effectiveness of vitamin A and cholecalciferol as wound-healing agents (45 FR 35656). In the tentative final monograph for OTC anorectal drug products, the agency agreed with the Panel's recommendations on vitamin A, cholecalciferol, and cod liver oil (53 FR 30756 at 30777).

Data on vitamin A and cholecalciferol as wound-healing agents were also submitted to the Miscellaneous External Panel. One manufacturer submitted data for a product containing in each ounce vitamin A and cholecalciferol equivalent to one ounce of cod liver oil (approximately 24,000 U.S.P. units vitamin A and 2,400 U.S.P. units cholecalciferol) in a vanishing cream base (Ref. 2). (One U.S.P. unit is identical to one IU (Ref. 3).) The submission was considered by the Panel in preparing its statement on OTC diaper rash drug products (47 FR 39436 at 39439), but the Panel did not classify any individual ingredients for this indication. The labeling states that the product is "for relief of chapped skin, diaper rash, wind burn and sunburn; and minor non-infected skin irritations." The directions for using the product to relieve minor skin irritations are "apply locally to unbroken skin with gentle massage or apply liberally to abraded skin surfaces where promotion of epithelization is desired."

The submission includes one article on diaper rash and prickly heat (Ref. 4) which states that preparations containing vitamin A and cholecalciferol were reported, in older literature, to promote healing and stimulate granulation, but that "it is difficult to substantiate this in modern literature." The submission also contains a published report of the successful use of a cod liver oil ointment in treating atopic eczema on a 15-month old boy.

The agency finds the submitted data are insufficient to support the use of vitamin A and cholecalciferol for diaper rash indications. The efficacy data pertain mainly to wound healing in adult subjects suffering from burns and other dermatologic conditions and to the use of vitamin A to treat acne in adolescents. There are no studies on the use of vitamin A or cholecalciferol for the treatment of diaper rash in infants and young children.

In this tentative final monograph, the agency is proposing a Category I classification of cod liver oil as a skin protectant ingredient for use in the treatment and prevention of diaper rash. (See comment 14 above.) This classification is based on the long marketing history of the safe use of cod liver oil as an ingredient in topical products used on infants and children and the Hemorrhoidal Panel's Category I recommendation of cod liver oil as a protectant ingredient. However, there is insufficient evidence to support the effectiveness of either vitamin A or cholecalciferol for use as an individual active ingredient or in combination other than as a component of cod liver oil in the treatment of diaper rash. The available data on the two ingredients

pertain to their use as wound-healing agents on adolescents and adults, not on infants and young children. These studies fail to establish that vitamin A and cholecalciferol contribute to wound healing. Further, the agency is not aware of any data that support the safety and effectiveness of wound-healing agents as components of OTC diaper rash drug products. The claim "promotes healing" has not been demonstrated in clinical studies for any ingredient contained in OTC diaper rash drug products.

Accordingly, the agency concludes that further data are needed to establish the effectiveness of vitamin A and cholecalciferol when used individually or in combination other than as a component of cod liver oil in OTC diaper rash drug products and classifies these ingredients in Category III for diaper rash use.

References

(1) "USAN and the USP Dictionary of Drug Names," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 122, 1989, s. v. "Cholecalciferol."

(2) OTC Volume 160028.

(3) "The United States Pharmacopoeia XXII—The National Formulary XVII," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 1473, 1989.

(4) Sadik, F., "Diaper Rash and Prickly Heat," in "Handbook of Non-Prescription Drugs," 1971 Ed., American Pharmaceutical Association, Washington, pp. 171–178, 1971.

V. Comment on Zinc Oxide

30. One comment requested that zinc oxide at an allowable dosage limit up to and including 40 percent be classified in Category I as a skin protectant for diaper rash. The comment noted that the Topical Analgesic Panel had recommended a dosage range of 1 to 25 percent for zinc oxide in its report on OTC skin protectant drug products (43 FR 34628 at 34648). The comment stated that data were submitted to the Miscellaneous External Panel to support the use of zinc oxide as a skin protectant in concentrations up to and including 40 percent (Ref. 1). The comment added that the minutes of the fourteenth meeting (November 12–13, 1976) of the Miscellaneous External Panel indicated that the Panel had recommended an upper limit of 40 percent for zinc oxide as a skin protectant (Ref. 2).

The Topical Analgesic Panel did not receive any data demonstrating the safety and effectiveness of zinc oxide as a skin protectant in concentrations above 25 percent. Based on the data available to it, that Panel recommended zinc oxide at a concentration up to and including 25 percent as a Category I skin protectant ingredient for use on infants, children, and adults (43 FR 34641). The agency concurred with this recommendation in its tentative final monograph for OTC skin protectant drug products (48 FR 6820 at 6832).

The data submitted to the Miscellaneous External Panel included information on an ointment containing 40 percent zinc oxide and 13.56 percent cod liver oil in a petrolatum base evaluated for the prevention or treatment of diaper rash. The submission for this product was referenced in appendix A to that Panel's minutes of its fourteenth meeting (Ref. 2). At that meeting, the Panel decided that zinc oxide at a concentration of 3 to 40 percent should be recommended as Category I for use as a protective, absorbent, and astringent. However, the Panel did not include this recommendation in its final report on OTC diaper rash drug products. The Panel chose instead to recommend the inclusion of zinc oxide for diaper rash claims in the rulemaking for OTC skin protectant drug products, but did not discuss a specific concentration for this or any other ingredient.

The submission includes an unpublished study using the ointment containing 40 percent zinc oxide (Ref. 3). In the study, 97 infants, age 12 months or younger, were assigned to one of two treatment groups. Group one received the ointment on an as needed basis. Group two received the same ointment six times a day. Biweekly examinations for diaper rash were made of the diaper area of each infant. Rashes were scored on a scale of zero (normal or no more than slight dryness) to four (pustules, excoriations, or other severe irritative conditions). The mothers were instructed to make no changes in any other aspect of baby-care except that no medicated lotions or powders were to be used. Neither group showed any evidence of an increase in irritation.

The submission also included an incomplete clinical study using the product for the treatment of diaper rash (Ref. 4). The study was considered incomplete because at the time it was submitted data were available for only thirty-five of the fifty cases discussed in the study. The additional data were submitted at a later date (Ref. 5). The study was completed on forty-five infants. Infants with an uncomplicated diaper rash were treated on either the right or left side of the diaper area with the product for 24 hours. The diaper area was divided into left and right sides with the umbilicus or vaginal folds anteriorly and the gluteal folds posteriorly designated as anatomic dividing lines, allowing each infant to be tested with the ingredient and compared with the control. The untreated side of the diaper area was permitted to be treated only with unmedicated talcum powder or bland soap. The severity of the rash was graded by a physician prior to initiation and at the completion of treatment using a scale of zero (absent) to five (severe). At the end of the treatment period, the physician also evaluated the difference between the treated and untreated side using a five-point scale ranging from one (much better) to five (much worse). The mothers also scored the severity of the rash at the initiation of treatment and at every diaper change on a scale from zero (none) to three (severe). The data showed that the treated side was significantly better than the untreated side on every measure. The only exceptions are the mothers' rating of severity of rash during the first eight hours after treatment began. No adverse reactions to the product were noted by either physician or mothers during the course of the study, and in no case was the treated side worse than the untreated side.

The agency believes that the studies discussed above support the safe use of 40 percent zinc oxide in an ointment dosage form. A review of the adverse reaction reports for zinc oxide and the 40 percent zinc oxide ointment product included in the agency's adverse drug reaction reporting system revealed only two minor adverse reactions (rash) to the ointment product (Ref. 6).

The agency has also considered the evaluation of zinc oxide done by the Miscellaneous External Panel at its fourteenth meeting (Ref. 2). That Panel concluded that zinc oxide crystals are not absorbed through the skin and pose no threat of systemic absorption with dermal application. Based on this conclusion, the Panel recommended no limit on zinc oxide dosage to body surfaces. However, the agency evaluated the nine OTC submissions cited in appendix A to the Panel's minutes and did not find any data to support the safe use of 40 percent zinc oxide on infants in other than an ointment dosage form. Because the agency is not aware of any data supporting the safe use of zinc oxide on infants at a concentration above 25 percent in any other dosage form, the agency is proposing to limit concentrations above 25 percent up to 40 percent zinc oxide to use in a suitable ointment dosage form as a Category I skin protectant ingredient for the prevention or treatment of diaper rash. Zinc oxide in 1 to 25 percent concentrations, as currently proposed in § 347.10(m), may be used in any

appropriate dosage form for a product intended to prevent or treat diaper rash.

References

(1) OTC Volume 160021.

(2) Summary Minutes of the Panel on Review of Miscellaneous External OTC Drug Products, Fourteenth Meeting, November 12 and 13, 1976, Docket No. 78N–0021, Dockets Management Branch.

(3) "Efficacy and Safety on Baby Ointment #0E14 for Leeming/Pacquin," draft of unpublished study, in OTC Volume 160021.

(4) "Desitin in the Treatment of Diaper Rash," Clinical Protocol Associates, Inc., draft of an unpublished study, in OTC Volume 160021.

(5) Comment No. C00058, Docket No. 78N–0021, Dockets Management Branch.

(6) Print-out of Adverse Drug Reactions to Cod Liver Oil, Zinc Oxide, and Desitin, January 17, 1990, Food and Drug Administration Adverse Drug Reaction Reporting System, in OTC Volume 06DRSTFM, Docket No. 78N–021D, Dockets Management Branch.

W. Comments on Drug Combinations

31. Two comments recommended a combination policy for diaper rash drug products similar to that contained in the Panel's proposed monograph for OTC skin protectant drug products (43 FR 34628 at 34631). The comments requested that a combination of two or more skin protectant ingredients be classified as Category I for treatment or prevention of diaper rash under the following conditions: (1) Each of the ingredients is present in sufficient quantity to act additively or by summation to produce the claimed therapeutic effect when present within the safe and effective concentration range specified for each ingredient in the monograph; (2) the ingredients do not interact with each other to reduce the effectiveness of any other ingredient(s) by precipitation, changes in acidity or alkalinity, or in some other manner that reduces the claimed therapeutic effect. One of the comments added that each ingredient or combination of ingredients must meet an appropriate level of effectiveness in treating or preventing diaper rash.

The Topical Analgesic Panel recommended that two or more skin protectant active ingredients may be combined provided the ingredients meet the conditions which are enumerated above, the partition of the active ingredients between the skin and the vehicle in which they are incorporated is not impeded, and the therapeutic effectiveness of each remains as claimed or is not decreased (43 FR 34631). In the tentative final monograph for OTC skin protectant drug products, the agency proposed various combinations of skin protectant active ingredients that varied depending on the labeling claims for the combinations. (See proposed § 347.20 at 48 FR 6832.) The use of skin protectant ingredients for the treatment and prevention of diaper rash was not discussed in that tentative final monograph, but is discussed in comment 8 above. In that comment, the agency states that an indication for treatment or prevention of diaper rash is being provided for those Category I skin protectant ingredients in § 347.10 that do not have a lower age limitation and that have a marketing history for such use, i.e., allantoin, calamine, dimethicone, kaolin, petrolatum, white petrolatum, and zinc oxide. (See detailed discussion in comment 8 above.) In addition, in this document, the agency is proposing the inclusion of additional ingredients in § 347.10 that were not included in the skin protectant tentative final monograph, i.e., cod liver oil, lanolin, mineral oil, talc, and topical starch. Some of these ingredients, such as cod liver oil and lanolin, are classified in Category I only when present in a combination product. (See comments 14 and 21 above.) Accordingly, the agency is proposing in this document to add new § 347.20(e) to the skin protectant tentative final monograph, to read as follows: "Any two or more of the ingredients identified in § 347.10 (a), (c), (e), (g), (h), (j), (m), (n), (o), (p), (q), (r), and (s) may be combined provided the combination is labeled according to § 347.50(b)(5) and provided each ingredient in the combination is within the concentrations specified in § 347.10."

32. One comment requested that the combination of a Category I antimicrobial agent and one or more Category I skin protectants be recognized as an acceptable Category I combination for the treatment and prevention of diaper rash. The comment contended that the antimicrobial agent would help reduce the level of harmful bacteria present in the diapered area and thus aid in the prevention and treatment of diaper rash. The comment suggested that indications for such a combination should include statements such as: "Helps kill germs associated with diaper rash" and "Helps kill germs that may aggravate diaper rash." Another comment mentioned that some diaper rash drug products contain ingredients that have not been classified in the skin protectant rulemaking, e.g., antimicrobials, antifungals, or external analgesics. The comment recommended that such ingredients must, first of all, have a record of safety for use on infants' skin and, secondly, when used in combination with a skin protectant for diaper rash, the combination product should meet the criteria established under each appropriate monograph.

The agency agrees with the second comment that each specific combination of one or more skin protectant ingredients and an ingredient other than a skin protectant must have established safety and effectiveness when used to treat or prevent diaper rash. As discussed elsewhere in this issue of the **Federal Register**, there are no antimicrobial, antifungal, or external analgesic active ingredients classified as Category I for the treatment and prevention of diaper rash.

Based on the status of the ingredients proposed in the notices of proposed rulemaking for OTC diaper rash drug products published in this issue of the **Federal Register**, combinations of a skin protectant active ingredient with other active ingredients are classified as follows: a skin protectant ingredient combined with another skin protectant ingredient, Category I; a skin protectant ingredient combined with an antimicrobial ingredient, Category III; a skin protectant ingredient combined with either an antifungal ingredient or an external analgesic ingredient, Category II.

33. A submission to the Miscellaneous External Panel (Ref. 1) included data to support the safety and effectiveness of a diaper rash cream containing a combination of dl-methionine,[1] cysteine hydrochloride, benzethonium chloride, talc, and a protein hydrolysate containing the amino acids 1-leucine, 1-isoleucine, 1-methionine, 1-phenylalanine, and 1-tyrosine. The submission was included in the list of submissions received by the Panel in its statement on OTC diaper rash drug products (47 FR 39439). The Panel considered the submission in preparing its statement but did not classify any individual ingredients for this indication.

The labeling for the product included in the submission stated that the product contained a germicide to help prevent irritation and amino acids to promote healing. Elsewhere in this issue of the **Federal Register**, the agency states its tentative conclusions on the use of antimicrobial ingredients for the treatment or prevention of diaper rash. In comment 32 above, the agency discusses combination products containing antimicrobial ingredients and skin protectant ingredients used for diaper rash. Talc is discussed in comment 28 above. The agency is addressing the use of amino acids in the

[1] Racemethionine is the official title in the 1989 edition of "USAN" and USP dictionary of drug names" and will be used in this document.

treatment or prevention of diaper rash in this comment.

The manufacturer cited the role of the amino acids methionine and cysteine and the protein hydrolysate in promoting wound healing as part of the basis for the formulation of the product. The manufacturer submitted in vitro data and animal studies to support the use of the amino acids methionine and cysteine in the regeneration of wound tissues and to show the effect of dietary deprivation of these amino acids on wound healing (Refs. 2 through 6). Based on animal studies by Edwards (Ref. 7) and other animal studies by Intoccia, Walsh, and Bogner (Ref. 8), the manufacturer concluded that both methionine and cysteine are relatively well absorbed following topical administration and are incorporated into body tissues.

The agency has reviewed the submission and concludes that the data are not sufficient to support a Category I classification for the topical use of amino acids to treat or prevent diaper rash. Susca and Geuting (Ref. 9) evaluated the total product, consisting of methionine, cysteine, protein hydrolysate, benzethonium chloride, and talc in a cream base, for the treatment of diaper rash against a placebo, consisting of the cream base without the active ingredients. Prior to using the product on infants with diaper rash, the authors tested the product for sensitizing potential by applying it to the arms and forearms of 25 infants and 25 children. On 20 occasions, the product was allowed to remain on the skin for at least 4 hours. No irritation was evident after 24 or 48 hours and no other side effects occurred. The agency notes that the article does not state whether or not occlusion was used to maintain the product in close contact with the skin. Therefore, the agency is not able to make any conclusions about the sensitizing potential of the product under the occlusive conditions found in the diaper area.

After the test for sensitizing potential was completed, the total product was applied to 52 infants and children (ranging in age from 6 days to 24 months) with diaper rash. Forty-seven of the children in the test group had a moderate degree of diaper rash characterized by marked erythema and papulovesicular lesions, two had a mild rash with few or no lesions, and three had severe rashes with ulcerations. The placebo group consisted of 50 children. No details concerning the makeup of this placebo group or the severity of the rashes in this group were provided. In 50 of the 52 subjects in the test group, the rashes receded after 48 hours and cleared after 5 days. The control group showed an overall lack of response to the placebo with few children showing slight improvement. Specific details on the response of the placebo group are not provided. No side effects were noted in any of the subjects in the study.

Christian and Gonzalez (Ref. 10) compared the same cream product for the treatment of diaper rash against a placebo consisting of fatty acid esters in a stabilized emulsion with a neutral pH. In this study, 36 infants (ranging in age from 5 days to 2 years) with diaper rashes ranging from mild to severe were treated with the cream product and 29 infants in the control group received the placebo. Both groups were balanced with regard to the severity of their rashes. In the placebo group, 13 cases showed complete or almost complete clearing, 8 cases showed moderate improvement, and 5 showed slight improvement, while 3 infants showed no improvement. In the test group, 30 cases showed complete or almost complete clearing while 6 showed moderate improvement. All the subjects in the test group showed some improvement. However, because the placebo used was not the cream base without the active ingredients, no conclusions regarding the contribution of the active ingredients to the effectiveness of the product can be made.

While the studies discussed above provide some evidence of the safe and effective use of the total cream product for the treatment of diaper rash, the data do not show (1) contribution of the individual amino acids to the effectiveness of the product, (2) contribution of the combination of amino acids to the effectiveness of the product, (3) contribution of the protein hydrolysate to the effectiveness of the product, and (4) whether the effectiveness shown resulted from the amino acid components of the product, from the talc, or from the antimicrobial benzethonium chloride. Therefore, the agency is classifying the individual ingredients racemethionine and cysteine hydrochloride; a protein hydrolysate composed of l-leucine, l-isoleucine, l-methionine, l-phenylalanine, and l-tyrosine; and the combination of these ingredients in Category III for safety and effectiveness for the treatment or prevention of diaper rash.

References

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(2) Layton, L.L., "In Vitro Sulfate Fixation by Granulation Tissue and Injured Muscle Tissue from Healing Wounds," Proceedings of the Society of Experimental Biology and Medicine, 73:570–572, 1950.

(3) Localio, S.A., L. Gillette, and J.W. Hinton, "The Biological Chemistry of Wound Healing—II. The Effect of dl-Methionine on the Healing of Surface Wounds," Surgery, Gynecology, and Obstetrics, 89:69–72, 1949.

(4) Perez-Tamayo, R., and M. Ihnen, "The Effect of Methionine in Experimental Wound Healing—A Morphologic Study," American Journal of Pathology, 29:233–243, 1953.

(5) Williamson, M.B., and H.J. Fromm, "The Incorporation of Sulfur Amino Acids into the Proteins of Regenerating Wound Tissue," Journal of Biological Chemistry, 212:705–712, 1955.

(6) Fromm, H.J., and R.C. Nordlie, "Experimental Injury and Sulfur Amino Acid Metabolism," Journal of Biological Chemistry, 223:737–741, 1956.

(7) Edwards, L.J., "The Absorption of Methionine by the Skin of the Guinea Pig," Biochemistry Journal, 57:542–547, 1954.

(8) Intoccia, A.P., J.M. Walsh, and R.L. Bogner, "Absorption and Incorporation of Methionine-S^{35} into Hair," Journal of Pharmaceutical Sciences, 53:372–375, 1964.

(9) Susca, L.A., and B.G. Geuting, "Treatment of Diaper Rash," New York State Journal of Medicine, 60:2858–2862, 1960.

(10) Christian, J.R., and F. Gonzalez, "Topical Treatment of Acute and Chronic Diaper Rash with Amino Acid Creme," Clinical Medicine, Vol. 8 (original article), 1961.

X. Comment on Testing

34. One comment suggested that the agency consider establishing a standard by which the effectiveness of diaper rash products may be determined for a claimed therapeutic benefit. The comment suggested a rating system, similar to the one that a panel recommended for sunscreen drug products at 43 FR 38265, as a way of measuring the levels of skin protection afforded by various diaper rash compositions. The comment recommended the following specific factors that might be considered in establishing the rating system: an ingredient's or combination of ingredients' tenacity and ability to adhere to the distressed diaper area, the degree of repellancy or insolubility afforded by a preparation, the viscosity or thickness of a preparation, intervals required between applications, and other physical and chemical properties of the preparation. The comment noted that while no research has specifically addressed these factors in connection with diaper rash preparations, studies have been made of the general properties of occlusive barrier ointments. The comment provided two published studies (Refs. 1 and 2) regarding the protectant characteristics of ointments which it felt offered a possible approach to the measurement of levels of skin protection afforded by diaper rash preparations. The comment

also proposed two clinical protocols to determine the effectiveness of diaper rash preparations: one for the prevention of diaper rash and the other for the treatment of existing diaper rash (Ref. 3).

The rating system for sunscreen drug products referred to by the comment was recommended by the Topical Analgesic Panel. That Panel stated that the extent of erythemal response to the sun is a function of skin color and identified five skin types that vary in their erythemal response to the sun (43 FR 38206 at 38210 and 38213). The "Sun Protection Factor" (SPF) was recommended by the Panel as a practical guide to aid the consumer in selecting the most suitable sunscreen for the level of sun protection suitable for his or her purposes. The Panel stated that the majority of consumers who use sunscreens have no pathological conditions, but desire to prevent a painful sunburn. The Panel further stated that individuals who are particularly susceptible to the immediate and cumulative effects of sunlight exposure should protect themselves from the harmful ultraviolet radiation from the sun (43 FR 38209). However, in the case of diaper rash, the agency believes that the consumer desires one level of protection, the complete protection of the infant's skin, whether dealing with a preexisting diaper rash or preventing a future rash. Therefore, the agency does not believe that a rating system, as suggested by the comment, would serve a useful purpose for OTC diaper rash drug products.

The agency has reviewed the two published studies (Refs. 1 and 2) submitted by the comment. The studies discuss a method for determining the protection afforded skin surfaces by various ointments. The basis for the method is the reaction of non-specific esterases found on the skin with 1-naphthylacetate to form 1-naphthol and acetic acid. The 1-naphthol formed by the reaction then can couple with the dye diazo blue B to form an azodye that stains the skin surface. Steigleder determined that this reaction is inhibited when an incubation medium containing 1-naphthylacetate and diazo blue B cannot make contact with the skin, *e.g.*, when the skin surface is covered with a protective ointment (Ref. 1).

In the other study, a glass chamber filled with an incubation medium containing 1-naphthylacetate and diazo blue B dye was placed on the skin surface of the forearms of 86 subjects following the application of various ointments. In each case, a control reaction was done on untreated skin of both forearms. The ointments were applied in two different ways: a "thin" application and a "thick" application (one to two millimeters thick). In addition, in some cases a thin layer of ointment was applied and wiped off, and in some other cases a thick layer of ointment was applied and rubbed into the skin 20 times. The glass chamber with the incubation medium was placed on the skin surface either immediately after the ointment was applied or following intervals varying between 30 and 120 minutes. Incubation times varied between 10 and 30 minutes.

The method discussed in the study measures the skin protection against water that is afforded by ointments in an almost static situation. However, diaper rash products are subject to exposure to urine and feces, increased temperature and humidity, and mechanical removal by friction. The agency believes that ointments tested by the proposed method would be substantially more effective than they would be under actual use conditions.

Further, the agency finds that the authors considered their method to be of limited usefulness. The authors stated that a detergent may remove esterases from the skin surface, and this test method should be avoided whenever substances are applied to the skin which inhibit the esterases or interfere with the formation of the azodye in the incubating medium. The agency also finds that this method, published over 25 years ago, does not appear to have gained general acceptance and usage in testing products for the degree of skin protection afforded. Therefore, the agency concludes that the method suggested by the comment would not be appropriate for establishing a rating system for diaper rash drug products.

The agency has reviewed the two proposed clinical protocols and finds them inadequate in several areas. In the protocol for treatment of diaper rash, no information is given about diaper rash variability in the infants to be studied, and the degree of difference between the effects of the treatments that will be considered clinically significant is not stated. Therefore, it cannot be determined whether a sample size of 25 infants is sufficient for the study. In addition, the proposed age span (0–24 months) does not take into consideration the difference in body chemistry among infants in this range of ages. An age range of 2 to 4 months may be more appropriate for a study of this type. Also, no consideration was given to the various types of diapers that may be used, the protocol lacked proper blinding, and specific instructions to the parents as to cleansing agent to use and amount of the product to apply were not provided. These inadequacies also apply to the proposed test for the prevention of diaper rash. In addition, it is unclear how this test will show effective "prevention" because the test subjects include infants who already have diaper rash. Further, the rationale for the use of a two-treatment, two-period crossover design was not presented.

The agency is not proposing 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 tentative final and final monographs will not include recommended testing guidelines for conditions that industry wishes to upgrade to 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 developing the final monograph. (See also part III, paragraph A. 2. below—Testing of Category II and Category III Conditions.)

References

(1) Steigleder, G.K., "A Method for Evaluating the Protection Afforded Skin Surfaces by Ointments," The Journal of Investigative Dermatology, 35:225–226, 1960.

(2) Steigleder, G.K., and W.P. Raab, "Skin Protection Afforded by Ointments," The Journal of Investigative Dermatology, 38:129–130, 1962.

(3) Comment No. C00030, Docket No. 78N–0021, Dockets Management Branch.

II. The Agency's Evaluation of the Submissions

Of the ingredients listed in the Miscellaneous External Panel's statement, the following are currently included in the rulemaking for OTC skin protectant drug products: allantoin, aluminum hydroxide, calamine, glycerin, petrolatum, shark liver oil, white petrolatum, and zinc oxide. The agency has reviewed the submissions to the Miscellaneous External Panel and determined that 15 submissions (Ref. 1) relate to products containing these ingredients with labeling claims for use in the treatment of diaper rash. Several submissions (Ref. 2) were for products containing lanolin, which was classified as an inactive ingredient by the Topical Analgesic Panel in its report on OTC skin protectant drug products (43 FR 34629). Three submissions included products containing vitamins A and D (Ref. 3), and two submissions included products containing mineral oil (Ref. 4). None of these ingredients was

individually classified by either Panel for use in diaper rash.

Several submissions (Ref. 5) were for products containing stabilized aloe vera for topical use for numerous indications including diaper rash, and one submission (Ref. 6) was for a product containing vitamin E for numerous skin conditions, including diaper rash. Subsequently, the manufacturers withdrew all of these submissions (Refs. 7, 8, and 9). Accordingly, the agency is not evaluating stabilized aloe vera and vitamin E in this rulemaking.

References

(1) OTC Volumes 160021, 160025, 160027, 160036, 160041, 160053, 160077, 160091, 160150, 160179, 160221, 160235, 160243, 160245, and 160357.

(2) OTC Volumes 160021, 160025, 160027, and 160179.

(3) OTC Volumes 160028, 160041, 160067, and 160179.

(4) OTC Volumes 160052 and 160086.

(5) OTC Volumes 160252, 160273, 160274, 160422, and 160423.

(6) OTC Volume 160067.

(7) Letter from B.C. Coats, Aloe Vera of America, Inc., to W. E. Gilbertson, FDA, dated April 5, 1983, in OTC Volume 06DRSTFM, Docket No. 78N-021D, Dockets Management Branch.

(8) Letter from A.J. Davis, Aloe Vera of America, Inc., to W. E. Gilbertson, FDA, dated October 24, 1986, in OTC Volume 06DRSTFM, Docket No. 78N-021D, Dockets Management Branch.

(9) Letter from S. Most, Block Drug Co., Inc., to Division of OTC Drug Evaluation, FDA, dated November 6, 1986, in OTC Volume 06DRSTFM, Docket No. 78N-021D, Dockets Management Branch.

III. The Agency's Tentative Conclusions and Adoption of the Panel's Statement

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

1. Summary of Ingredient Categories

Although the Panel discussed the use of skin protectant ingredients for the treatment of diaper rash, it did not review or classify any individual ingredients. All ingredients in marketed products submitted to the Panel or ingredients that appeared in the call-for-data notices were simply listed in the Panel's statement on OTC drug products for the treatment of diaper rash (47 FR 39436 at 39439). The Panel recommended that the use of skin protectant ingredients included in this list be referred to the rulemaking for OTC skin protectant drug products and requested comments from any interested person on the use of any of these ingredients for the treatment of diaper rash.

The agency has reviewed all claimed active ingredients submitted to the Miscellaneous External Panel, the recommendations of the Topical Analgesic Panel on OTC skin protectant drug products (43 FR 34628), the tentative final monograph on OTC skin protectant drug products (48 FR 6820), and other data and information available at this time. Based upon this information, the agency is proposing the following categorization of skin protectant active ingredients for the treatment and prevention of diaper rash:

Ingredient	Category
Aldioxa	III
Allantoin	I
Aloe vera [1]	N/A
Aluminum acetate	III
Aluminum hydroxide	III
Bismuth subnitrate	III
Boric acid	II
Calamine	I
Casein (calcium casinate) [1]	N/A
Cellulose, microporous	III
Cholecalciferol	III
Cocoa butter	III
Cod liver oil (in combination)	I
Colloidal oatmeal	III
Cysteine hydrochloride	III
Dexpanthenol	III
Dimethicone	I
Glycerin	III
Kaolin	I
Lanolin (in combination)	I
Live yeast cell derivative	III
Mineral oil	I
Peruvian balsam	III
Peruvian balsam oil	III
Petrolatum	I
Protein hydrolysate (1-leucine, 1-isoleucine, 1-methionine, 1-phenylalanine, and 1-tyrosine).	III
Racemethionine	III
Shark liver oil	III
Sodium bicarbonate	III
Sulfur	II
Talc	I
Tannic acid	II
Topical starch	I
Vitamin A	III
Vitamin E [1]	N/A
White petrolatum	I
Zinc acetate	III
Zinc carbonate	III
Zinc oxide	I

[1] Not classified—withdrawn from review.

2. Testing of Category II and Category III Conditions

The agency is not proposing specific testing guidelines in this document. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any 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) and clarified April 1, 1983 (48 FR 14050). That policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of Agency's Changes

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the substance of the Panel's statement. In the absence of a specific monograph recommendation from the Panel, the agency has developed a monograph based on its evaluations of the data and its responses to the comments above and below.

The agency has revised the Panel's definition of diaper rash, which was as follows:

> Diaper rash is a common skin problem of infancy, caused by contact with urine and feces, worsened by occlusion with plastic pants, and often secondarily infected with *Candida albicans*. (See 47 FR 39440.)

One comment noted that diaper rash is perhaps best viewed as a group of disorders rather than a specific diagnosis. The comment stated that the condition commonly referred to as diaper rash is an acute, inflammatory reaction of the skin in the diaper area, which may range from mild (characterized by mild erythema with or without chafing) to severe (characterized by vesicles, pustules, or bullae). The comment added that mild diaper rash is primarily caused by one or more diverse chemical and mechanical irritants. The comment stated that a major cause of diaper rash is the exposure of tender skin for relatively long periods of time to moisture from urine and to feces, with this exposure taking place in an enclosed, humid area. The skin is hydrated and susceptible to frictional irritation as well as chemical irritation.

In reviewing numerous articles on diaper rash that have appeared in the literature (Refs. 1 through 12), the agency notes that various authors have defined diaper rash in different ways. The agency has evaluated these, the Panel's, and the comment's definitions and is proposing the following definition in § 347.3 of this tentative final monograph:

Diaper rash or diaper dermatitis. An inflammatory skin condition in the diaper area (perineum, buttocks, lower abdomen, and inner thighs) caused by one or more of the following factors: moisture, occlusion, chafing, continued contact with urine or feces or both, or mechanical or chemical irritation. Mild conditions appear as simple erythema. More severe conditions include papules, vesicles, oozing, and ulceration.

References

(1) Arndt, K., "Diaper Rash" in "Manual of Dermatologic Therapeutics—With Essentials of Diagnosis," 2d Ed., Little, Brown and Co., Boston, p. 66–69, 1978.

(2) Brown, M.S., "Over-the-Counter Drugs for Skin Disorders—Part 3: Aids for Heat and Diaper Rash," Nurse Practioner, July/August: 28–29, 1977.

(3) Gossel, T.A., "Diaper Dermatitis," U. S. Pharmacist, 9:34–40, 1984.

(4) Honig, P.J., "Diaper Dermatitis," Postgraduate Medicine, 74:79–88, 1983.

(5) Leyden, J.J., "Diaper Dermatitis," Dermatologic Clinics, 4:23–28, 1986.

(6) Sadik, F., "OTC Products for Diaper Rash and Prickly Heat," Journal of the American Pharmaceutical Association, 1:19–24, 1970.

(7) Schanzer, M.C., and J.K. Wilkin, "Diaper Dermatitis," American Family Physician, 25:127–132, 1982.

(8) Smith, G.H., "Chapter 32—Diaper Rash and Prickly Heat Products," in "Handbook of Nonprescription Drugs," 8th Ed., American Pharmaceutical Association, Washington, pp. 643–653, 1986.

(9) Weinberg, S., and R.A. Hoekelman, "Pediatric Dermatology for the Primary Care Practitioner," McGraw-Hill, New York, p. 121, 1979.

(10) Weston, W.L., "Practical Pediatric Dermatology," Little, Brown and Co., Boston, pp. 51–53, 1979.

(11) Williams, M.L.K., "How I Treat Diaper Rashes," Medical Times, 108:50–53, 1980.

(12) Zimmerman, D.R., "Diaper-Rash Medications," in "The Essential Guide to Nonprescription Drugs," Harper and Row, New York, p. 228–237, 1983.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule for OTC skin protectant drug products for the treatment or prevention of diaper rash, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act (Pub. L. 96–354). That assessment included a discretionary regulatory flexibility analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC skin protectant drug products for the treatment or prevention of diaper rash is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC skin protectant drug products for the treatment or prevention of diaper rash. 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 for the treatment or prevention of diaper rash 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 for the treatment or prevention of diaper rash, a period of 180 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 invited public comment in the advance notice of proposed rulemaking regarding any impact that this rulemaking would have on OTC skin protectant drug products used for the treatment of diaper rash. No comments on economic impacts were received. Any comments on the agency's initial determination of the economic consequences of this proposed rulemaking should be submitted by December 17, 1990. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined under 21 CFR 25.24(c)(6) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Interested persons may, on or before December 17, 1990, 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 rulemaking. 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 December 17, 1990. 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 June 20, 1991, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before August 20, 1991. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (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 for OTC skin protectant drug products, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on August 20, 1990. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph for OTC skin protectant drug products is published in the **Federal Register**, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

List of Subjects in 21 CFR Part 347

Labeling, Over-the-counter drugs, Skin protectants.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, it is proposed that subchapter D of chapter I of title 21 of the Code of Federal Regulations be amended in part 347 as

proposed in the **Federal Register** of February 15, 1983, 48 FR 6820; and further amended by the **Federal Register** of April 3, 1989, 54 FR 13490; the **Federal Register** of October 3, 1989, 54 FR 40808; and the **Federal Register** of January 31, 1990, 55 FR 3362 as follows:

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

1. The authority citation for 21 CFR part 347 is revised to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

2. In subpart A, § 347.3(e) is added to read as follows:

§ 347.3 Definitions.

* * * * *

(e) *Diaper rash or diaper dermatitis.* An inflammatory skin condition in the diaper area (perineum, buttocks, lower abdomen, and inner thighs) caused by one or more of the following factors: moisture, occlusion, chafing, continued contact with urine or feces or both, or mechanical or chemical irritation. Mild conditions appear as simple erythema. More severe conditions include papules, vesicles, oozing, and ulceration.

3. In subpart B, § 347.10 (n), (o), (p), (q), (r), and (s) are added to read as follows:

§ 347.10 Skin protectant active ingredients.

* * * * *

(n) Cod liver oil, 5 to 13.56 percent in accordance with § 347.20(e) and provided the product is labeled so that the amount of the product that is used in a 24-hour period represents a quantity that does not exceed 10,000 U.S.P. units of vitamin A and 400 U.S.P. units of cholecalciferol.

(o) Lanolin, 15.5 percent in accordance with § 347.20(e).

(p) Mineral oil, 50 to 100 percent.

(q) Talc, 45 to 100 percent.

(r) Topical starch, 10 to 98 percent.

(s) Zinc oxide, above 25 to 40 percent in an ointment dosage form.

4. In subpart B, § 347.20(e) is added to read as follows:

§ 347.20 Permitted combinations of active ingredients.

* * * * *

(e) Any two or more of the ingredients identified in § 347.10 (a), (c), (e), (g), (h), (j), (m), (n), (o), (p), (q), (r), and (s) may be combined provided the combination is labeled according to § 347.50(b)(5) and provided each ingredient in the combination is within the concentrations specified in § 347.10.

5. In subpart C, § 347.50 is amended by revising the introductory text of paragraph (b), by adding paragraphs (b)(5) and (c)(10), by revising paragraph (d) introductory text and paragraph (d)(1), and by adding paragraph (d)(4) to read as follows:

§ 347.50 Labeling of skin protectant drug products.

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(b) *Indications.* The labeling of the product states under the heading "Indications" one or more of the phrases listed in this paragraph (b) of this section, as appropriate. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in paragraph (b) of this section, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the Federal Food, Drug, and Cosmetic Act (the act) against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

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(5) *For products containing any ingredient in § 347.10 (a), (c), (e), (g), (h), (j), (m), (n), (o), (p), (q), (r), and (s).* "Helps treat and prevent diaper rash. Protects" (select one of the following: "chafed skin" or "minor skin irritation") (select one of the following: "due to" or "associated with") "diaper rash and helps" (select one of the following: "protect from" or "seal out") "wetness."

(c) * * *

(10) *For powder products containing kaolin identified in § 347.10(g), topical starch identified in § 347.10(r), or talc identified in § 347.10(q).* "Do not use on broken skin. Keep powder away from child's face to avoid inhalation, which can cause breathing problems."

(d) *Directions.* The labeling of the product contains the following statements, as appropriate, under the heading "Directions:"

(1) *For products labeled according to § 347.50(b) (1), (2), or (3).* "Apply liberally as often as necessary."

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(4) *For products labeled according to § 347.50(b)(4)—(i) For all products.* "Change wet and soiled diapers promptly, cleanse the diaper area, and allow to dry. Apply" (select one of the following: "ointment," "cream," "powder," or "product") "liberally as often as necessary, with each diaper change, especially at bedtime or anytime when exposure to wet diapers may be prolonged."

(ii) *For powder products only.* "Apply powder close to the body away from child's face. Carefully shake the powder into the diaper or into the hand and apply to diaper area."

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Dated: April 24, 1990.

James S. Benson,

Acting Commissioner of Food and Drugs.

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