DEPARTMENT OF HEALTH AND HUMAN SERVICES

21 CFR Part 348

[Docket No. 78N-301D]

RIN 0905-AA06

External Analgesic 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 notice of proposed rulemaking for over-the-counter (OTC) external analgesic drug products. (See the **Federal Register** of February 8, 1983; 48 FR 5852.) This part of the proposed rulemaking concerns conditions under which OTC external analgesic drug products for the treatment or prevention of diaper rash are not generally recognized as safe and effective, and are 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 and public comments on an advance notice of proposed rulemaking that was based on that statement. 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 external analgesic 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.

Seven 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 except one comment which was submitted to the external analgesic rulemaking only. All of the overlapping comments were submitted to the rulemaking for OTC skin protectant drug products. In those cases where the same comments were submitted to more than one rulemaking, the comments are being addressed only once—in the 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 this notice of proposed rulemaking, FDA responds to public comment and states for the first time its position on OTC external analgesic 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 external analgesic 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 skin protectant 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 external analgesic 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 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 notice 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 the notice of proposed rulemaking to amend the tentative final monograph for OTC skin protectant drug products, published elsewhere in this issue of the **Federal Register**.

Regarding those portions of the comments that concerned external analgesic active ingredients, 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 (February 15, 1983; 48 FR 6820 at 6830), 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 that baking soda should be considered in both rulemaking.

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 the Panel had discussed in that rulemaking (e.g., for the temporary relief of pain and itching due to minor burns, sunburn, * * * insect bites, and minor skin irritations), those uses for sodium bicarbonate would more appropriately be addressed 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, as discussed elsewhere in this issue of the **Federal Register**, 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.

Another comment, in discussing the Panel's referral of diaper rash ingredients to the various rulemakings, noted that some of the ingredients which are not skin protectants are classified as irritants that may indeed be found harmful when used in the diaper area. The comment added that this would be especially true of many of the referred external analgesic ingredients. This is discussed in Part III. below—The Agency's Tentative Conclusions and Adoption of the Panel's Statement.

Another comment, submitted only to the external analgesic rulemaking, suggested that the indications in the tentative final monograph in proposed § 348.50(b)(4) (48 FR 5852 at 5868) be revised in order to state more clearly the uses for which aluminum acetate solution is recommended. Part of the proposed revision would read: "a soothing wet dressing for relief of skin irritations" caused by various conditions including diaper rash. The agency believes that "relief of skin irritations" is basically a skin protectant claim, therefore, this comment is more appropriately addressed in the rulemaking for OTC skin protectant drug products for diaper rash. (See discussion of aluminum acetate used as a skin protectant, published elsewhere in this issue of the **Federal Register**.)

One additional 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."

In this document, the agency is addressing only one aspect of the comment's request: The antipruritic (anti-itch) use of colloidal oatmeal as it pertains to diaper rash. The agency will address the antipruritic use of colloidal oatmeal for the other conditions stated above in a future **Federal Register** publication pertaining to the rulemaking for OTC external analgesic drug products. The agency discussed the skin protectant use of colloidal oatmeal for providing skin protection and relieving minor irritation and itching due to poison ivy, poison oak, poison sumac, and insect bites in the notice of proposed rulemaking amending the tentative final monograph for OTC skin protectant drug products. (See 54 FR 40808 at 40809 to 40811; October 3, 1989.)

As stated in Part III. below—The Agency's Tentative Conclusions and Adoption of the Panel's Statement, the agency has determined that external analgesic active ingredients should not be included in OTC diaper rash drug products because infants and young children (the target population for these products) would not be able to communicate verbally their symptoms to a parent and, thus, the need for an anti-itch external analgesic ingredient could not be appropriately determined. However, the fact that colloidal oatmeal cannot be used in an OTC diaper rash drug product bearing an anti-itch claim does not prevent colloidal oatmeal from being used in an OTC diaper rash drug product bearing only skin protectant

claims. (See the discussion of colloidal oatmeal used as a skin protectant in the notice of proposed rulemaking to amend the tentative final monograph for OTC skin protectant drug products published elsewhere in this issue of the Federal Register.)

II. The Agency's Evaluation of the Submissions

Of the ingredients listed in the Panel's statement on OTC drug products for diaper rash, the following are currently included in the rulemaking for OTC external analgesic drug products: Benzocaine, camphor, dibucaine, eucalyptol, hydrocortisone acetate, menthol, oil of cade, oil of eucalyptus, phenol, pramoxine, resorcinol, and tetracaine (47 FR 39415 and 39416). The agency has reviewed the submissions to the Panel and determined that only three submissions were for products that contained one or more of the above ingredients with labeling claims for use in the treatment of diaper rash (Refs. 1, 2, and 3).

One submission was for a combination product containing the ingredients methylbenzethonium chloride, zinc oxide, calamine, and eucalyptol. These ingredients were identified in the labeling submitted (Ref. 1), and the product was promoted as a "diaper rash ointment." However, the active ingredient section of the submission did not identify eucalyptol as an active ingredient, and the submission did not contain any safety or efficacy data on the use of eucalyptol as an external analgesic active ingredient to prevent or treat diaper rash. The ingredient methylbenzethonium chloride is discussed in the proposed rulemaking for OTC antimicrobial diaper rash drug products, and the ingredients calamine and zinc oxide are discussed in the proposed rulemaking for OTC skin protectant diaper rash drug products, published elsewhere in this issue of the Federal Register.

The second submission was for a combination product for which the manufacturer claimed nine active ingredients, two of which were juniper tar (oil of cade) and resorcinol (Ref. 2). However, the submission did not contain any specific information on the safety and efficacy of juniper tar and resorcinol as external analgesic active ingredients for use in diaper rash. Based on the product's current labeling (Ref. 3), the product has been reformulated and no longer contains juniper tar.

The third submission was for a combination product containing two percent dexpanthenol, 0.1 percent menthol, and 0.1 percent camphor labeled for "relief of itching and discomfort in minor skin disorders" and "useful in diaper rash" (Ref. 4). Effectiveness data pertaining to diaper dermatitis consisted of two reports of clinical experience using a cream containing dexpanthenol to treat diaper dermatitis (Refs. 5 and 6). In one report, it was noted that the combination product reduced inflammation within 24 hours after initiation of treatment, i.e., application of the product to the affected areas each time the diaper was changed (Ref. 5). In the second report, based on 12 years of clinical experience using a cream containing pantothenylol, it was noted that 23 out of 28 cases of diaper dermatitis were treated with satisfactory results, while 5 of the 28 cases resulted in unsatisfactory results (Ref. 6). [Pantothenylol is now known as dexpanthenol (Ref. 7).] In both reports, the amount of data presented is very limited. Further, both reports make reference to use of a combination product. Neither report provides any evidence to establish that the menthol or camphor component contributed to the results observed.

The agency concludes that the submissions made to the Panel are inadequate to establish the safety and effectiveness of any OTC external analgesic active ingredient for the treatment or prevention of diaper rash.

References

(1) OTC Volume 160027.

(2) OTC Volume 160040.

(3) Letter from J.A. Devaney, The Mentholatum Co., Inc., to L. Geismar, FDA, October 23, 1986, OTC Volume 06DRETFM, Docket No. 78N–301D, Dockets Management Branch.

(4) OTC Volumes 160104 and 160204.

(5) Dubow, E. "Ammoniacal Napkin Dermatitis in Infants," *Archives of Pediatrics*, 71:323–326, 1954.

(6) Kline, P.R., "12 Years Experience Using Panthothenylol Topically," *Western Medicine*, 4:78, 1963.

(7) Budavari, S., editor," "The Merck Index," 11th Ed., Merck & Co., Inc., Rahway, NJ, 1989, s.v. "dexpanthenol."

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

Although the Panel discussed the use of external analgesic 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 notice were simply listed in the Panel's statement on OTC drug products for the treatment of diaper rash (47 FR 39412 at 39415). The Panel recommended that the use of external analgesic ingredients included in this list be referred to the rulemaking for OTC external analgesic drug products and requested comments from any interested person on the use of any of these ingredients for the treatment of diaper rash.

As discussed above, only three of the comments addressed the use of external analgesic active ingredients in diaper rash drug products. The agency has determined that the use of these ingredients—sodium bicarbonate, aluminum acetate, and colloidal oatmeal—for the treatment or prevention of diaper rash is more appropriately addressed in the rulemaking for OTC skin protectant drug products.

The other data submitted have been inadequate to support the use of any other external analgesic active ingredients in the treatment or prevention of diaper rash.

In the tentative final monograph for OTC external analgesic drug products, the agency stated that external analgesic active ingredients are intended for the relief of pain and/or itching, or for the relief of minor aches and pains (48 FR 5852 at 5868). The agency also stated that these ingredients should not be used on children under 2 years of age except as recommended by a physician in order to provide an adequate margin of safety (48 FR 5869). The agency discussed the possibility of cutaneous absorption due to occlusion of the skin, as from a diaper or from lying on a waterproof mattress or from body folds touching each other, and mentioned that analgesic drugs can also be corrosive to infants' skin under occlusion (48 FR 5864). The agency added that children at the age of 2 years are just beginning to learn to communicate verbally in expressing their symptoms to a parent, whereas children below the age of 2 years are more passive and less able to express and localize symptoms [to a parent]. In addition, as one comment noted, many external analgesic active ingredients are classified as irritants that may be harmful when used in the diaper area. For these reasons, the agency does not believe that external analgesic active ingredients should be present in OTC diaper rash drug products. In addition, there is a lack of data to show that any OTC external analgesic active ingredients are generally recognized as safe and effective for the treatment or prevention of diaper rash. The agency therefore is proposing that OTC drug products labeled for the treatment and/or prevention of diaper rash be formulated to contain no external analgesic ingredients.

Accordingly, based on all information available to date, the agency is

proposing that any OTC external analgesic drug product labeled for the treatment and/or prevention of diaper rash is not generally recognized as safe and effective. If this proposal is ultimately adopted, upon the effective date of that portion of the final rule for OTC external analgesic drug products that applies to OTC diaper rash drug products, any OTC drugs containing external analgesic active ingredients and labeled for the treatment and/or prevention of diaper rash that are initially introduced or initially delivered for introduction into interstate commerce would be regarded as unapproved new drugs and subject to regulatory action. Manufacturers are encouraged to comply voluntarily with the proposed rule at the earliest possible date.

The agency emphasizes that the final rule for OTC external analgesic drug products, as it relates to OTC diaper rash drug products, will not apply to (1) active ingredients included in the external analgesic final monograph that are Category I antipruritics for claims other than diaper rash and (2) active ingredients included in both the external analgesic and skin protectant rulemakings where the ingredient is a Category I skin protectant making allowable diaper rash skin protectant claims, e.g., sodium bicarbonate.

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 external analgesic 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 external analgesic 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 external analgesic 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 external analgesic 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 external analgesic 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 external analgesic 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 external analgesic drug products, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on August 20, 1991. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph for OTC external analgesic drug products is published in the **Federal Register**, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Dated: April 24, 1990.

James S. Benson,

Acting Commissioner of Food and Drugs.

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