OTC topical antifungal 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 topical antifungal 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 topical antifungal 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 topical antifungal 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 topical antifungal 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 topical antifungal 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 am. and 4 pm., 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 topical antifungal 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 topical antifungal drug products is published in the **Federal Register**, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Dated: April 24, 1999.

James S. Benson,

Acting Commissioner of Food and Drugs.

[FR Doc. 90–13650 Filed 6–19–90; 8:45 am]

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Wednesday
June 20, 1990

Part V

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 333

Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Proposed Rule for Diaper Rash Drug Products

DEPARTMENT OF HEALTH AND HUMAN SERVICES

21 CFR PART 333

[Docket No. 75N-183D]

RIN 0905-AA06

Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Proposed Rulemaking for Diaper Rash Drug Products

AGENCY: Food and Drug Administration.

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) topical antimicrobial drug products. The proposed rulemaking would establish conditions under which OTC topical antimicrobial 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 topical antimicrobial drug products. (See the **Federal Register** of January 6, 1978; 43 FR 1210.) 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 topical antimicrobial 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.

Four 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 the notice of proposed rulemaking to amend the notice of proposed rulemaking for OTC skin protectant drug products. In addition, this document addresses comments on products containing topical antimicrobial ingredients used for diaper rash that were submitted by two drug manufacturers in response to the advance notice of proposed rulemaking for OTC topical antimicrobial drug products (see the **Federal Register** of September 13, 1974; 39 FR 33103) and the tentative final monograph for OTC topical antimicrobial drug products (see the **Federal Register** of January 6, 1978; 43 FR 1210). Copies of the comments received are on public display in the Dockets Management Branch (address above).

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 topical antimicrobial 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 topical antimicrobial drug products for use in diaper rash. Other documents concerning the use of OTC topical antifungal drug products, OTC external analgesic 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 topical antimicrobial 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. For example, 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 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. Those comments are incorporated by reference into this rulemaking.

A. General Comments on Antimicrobial Ingredients in Diaper Rash Drug Products

1. Several comments stated that OTC topical antimicrobial ingredients can provide rational therapy to prevent or treat diaper rash by reducing the level of harmful bacteria present in the diapered area. One comment suggested that indications for an antimicrobial-containing diaper rash drug product should include such statements as "helps kill germs associated with diaper rash" and "helps kill germs that may aggravate diaper rash." Another comment stated that secondary infections caused by bacteria or fungus may accompany diaper rash as complications, and these infections should be diagnosed and treated by a physician. The comment contended that OTC drug products are useful to protect the skin from the irritation of urine and feces, but not to treat the secondary infection that may accompany the irritation.

The agency agrees with the last comment. Only ordinary, mild diaper rash (in which the skin is reddened but not broken) should be treated with OTC drugs. A rash in the diaper area that does not clear up in a reasonable amount of time may indicate the presence of a secondary bacterial or fungal skin infection (Refs. 1 and 2). The agency believes that these conditions should not be treated with OTC drugs and that an infant with a suspected bacterial infection in the diaper area or a diaper rash that has persisted a week or more should be taken to a physician for appropriate diagnosis and therapy. Some physicians recommend treating bacterial infections in the diaper area with systemic antibiotics (Refs. 2, 3, and 4), which require a physician's prescription. (See fungal infections in diaper rash as discussed in the notice of proposed rulemaking for OTC antifungal drug products published elsewhere in this issue of the Federal Register.)

Diaper dermatitis is a convenient term used to encompass a wide range of inflammatory processes that occur in the diaper area (Ref. 5). Diaper dermatitis includes diverse disorders which appear in the diaper area, and identifying the etiology of a diaper rash and selecting the therapeutic agent are difficult even for a physician (Refs. 2 through 6). Schanzer and Wilkin (Ref. 2) noted that the diagnostic range includes irritant dermatitis, allergic dermatitis, intertrigo, seborrheic dermatitis, atopic eczema, candidiasis, psoriasis, scabies, miliaria, bullous impetigo, and granuloma gluteal infantum. These authors developed a full page flow chart to be used by family physicians for diagnosing and treating diaper dermatitis before referring a patient to a dermatologist.

The agency agrees with these experts (Refs. 2 through 6) that lay persons do not have adequate medical background or training to diagnose and treat such infections or other conditions in the diaper area. The agency believes that a physician should be consulted for diagnosis and appropriate therapy for the different types of diaper dermatitis described above, including bacterial infection. Accordingly, the agency believes the claim "treats infection" or any similar claim is inappropriate for OTC diaper rash drug products and should be classified Category II.

As to general antimicrobial claims, such as "helps kill germs associated with diaper rash," the agency notes that a number of diaper rash products submitted to the OTC drug review contain antimicrobial ingredients such as boric acid, calcium undecylenate, methylbenzethonium chloride, sodium propionate, and triclosan. These products include antimicrobial labeling such as "antiseptic," "for diaper rash: acts as antiseptic to help fight staph germs and other bacteria," "kills millions of diaper rash germs," "kills bacteria that cause diaper rash and odor," and "medicated formula, inhibits the growth of bacteria." These claims are discussed below.

The agency has evaluated the role of bacteria in causing or aggravating diaper rash. As noted above, secondary infections, usually due to *Staphylococcus aureus (S. aureus)*, streptococci, or *Candida albicans (C. albicans)* (Ref. 2), may develop as a complication of diaper rash. It is much less clear, however, what changes in the normal skin flora may accompany diaper rash that could predispose to the development of a secondary infection or whether the use of OTC antimicrobial ingredients is effective in preventing secondary infections. The data submitted do not adequately address these questions because many of the

studies were in vitro studies on the antibacterial activity of the ingredient and did not address the issue of bacterial involvement in diaper dermatitis or demonstrate clinical effectiveness. Furthermore, even the clinical studies which demonstrated improvement did not include microbiological cultures from the treated infants to determine whether the improvement could be attributed to the antimicrobial ingredient. The studies are discussed as part of the individual ingredient evaluations later in this document.

The agency has identified several microbiological studies in which infants with and without diaper rash were compared to determine the role of bacteria in causing diaper rash (Refs. 7 through 11). In some of the studies described below, the normal infants have similar and sometimes higher total bacterial counts or larger number of species isolated than the infants with diaper rash. It could be argued, therefore, that proliferation of bacteria does not appear to be a cause of diaper rash. One persistent finding in many of the studies is that the counts of *S. aureus* are higher in the infants with diaper rash than in the normal control infants or the after-cure infants.

Brookes, Hubbert, and Sarkany (Ref. 7) studied 60 infants on their regular well baby visits to a family health clinic to determine the incidence of diaper rash and to clinically evaluate early cases. A wide range of bacteria was found on the skin of both groups of infants with a total of 9 bacterial species for the normal group and 7 for the diaper rash group. However, no significant difference was found in the microflora of the skin in the diaper area of 25 infants with diaper dermatitis and 35 normal infants. Overall, an average of 2.6 species were cultured from the normal infants and 2.4 bacterial species from the infants with diaper rash. The incidence of *S. aureus* (or coagulase positive staphylococci) was 20 percent in both groups. The authors added that they had included in their study only infants in which diaper rash was an incidental finding and concluded that the state of the bacterial skin flora plays no etiological role in early cases of diaper rash.

Brown, Tyson, and Wilson (Ref. 8) conducted a bacteriological survey of the types of organisms found in wet diapers, soiled diapers, and from swab cultures taken from 81 children with diaper rash and 25 children not having rash. Thirteen species of bacteria were isolated from the infants with diaper rash and 10 species from the control infants. *Escherichia coli* (*E. coli*) was the most frequent isolate, occurring in all 25 of the control infants and in 77 (95 percent) of the infants with diaper rash. Major differences in the two groups occurred with *S. aureus* which was isolated from 52 (64.2 percent) of the infants with diaper rash but only from 1 (4 percent) of the infants not having a rash. Beta hemolytic streptococci were isolated from 21 (25.9 percent) of the infants with diaper rash and from 2 (8 percent) of the control infants. *Streptococcus viridans* (*S. viridans*) occurred frequently in both groups, but was still more prevalent in the infants with diaper rash (81.5 percent) than in the control infants (48 percent). Six children in the control group had previously been studied while they had diaper rash; *S. aureus* was isolated from two children. The organisms were not isolated following recovery.

Pittillo et al. (Ref. 9) studied the microbial skin flora of the diaper area of 10 infants without a recent history of diaper dermatitis and 10 infants affected with diaper dermatitis. Eleven different bacterial species were recovered from the normal group, and nine from the group with diaper rash. Overall, an average of 2.4 species was cultured from the infants with diaper rash and 2.9 species from the normal infants. The incidence of *E. coli* was the most striking difference, occurring in 8 out of 10 of the normal infants but in only 3 out of 10 of the infants with diaper rash. *S. aureus* occurred in 5 out of 10 of the infants with diaper rash, but occurred only in 3 of 10 of the normal infants.

Leyden and Kligman (Ref. 10) conducted a quantitative microbiological survey of multiple sites in the diaper area in 40 normal infants and 100 infants with various forms of diaper dermatitis, classified clinically into the following categories: chafing dermatitis (20 percent), atopic dermatitis (24 percent), moniliasis (25 percent), moniliasis with disseminated "id" (15 percent), seborrheic dermatitis (10 percent), psoriasis (2 percent), and undecided (4 percent). The authors stated that chafing (irritant) rash is the most prevalent and the least serious form of diaper dermatitis, and it is usually treated without medical advice. Although *S. aureus* was not recovered from any site of the normal infants, it was frequently isolated from the infants with diaper dermatitis. *S. aureus* occurred in all of the cases of atopic dermatitis type diaper rash and made up 80 percent of the total flora. *S. aureus* also was frequently found at lower counts in the other types of diaper dermatitis including 50 percent of the infants with chafing dermatitis in which it made up 20 percent of the total flora when present. The authors considered *S. aureus* to be a secondary invader in atopic dermatitis in the diaper area. Conversely, because the level of *S. aureus* was lower in chafing diaper dermatitis, Leyden and Kligman concluded that microbes appear to play no role in the chafing form of diaper dermatitis, which they considered to result from friction and maceration of constantly wet skin.

Montes et al. (Ref. 11) obtained bacterial cultures from the diaper area of 35 infants with diaper dermatitis and from 25 normal controls. A total of 14 species of microorganisms were recovered in the diaper rash group, 13 in the normal control group. The average number of species per infant was 2.54 for the diaper rash group, and 2.36 for the normal control group. The authors found that *S. aureus* and *Aerobacter aerogenes* occurred significantly more often in the diaper rash group than in the normal control group. *S. aureus* was recovered from 42.8 percent of the infants with diaper rash, and 28 percent of the normal control infants. For the other 12 species of bacteria recovered in the study, the normal control group had just as high, if not higher, an incidence as the diaper rash group. There was no significant difference in the total microbial counts of the two groups.

The agency has determined that more information is needed to clarify what, if any, role specific bacteria such as *S. aureus* play in ordinary, mild diaper rashes (where the skin is reddened but not inflamed or infected) that would be suitable for OTC drug treatment.

Leyden and Kligman (Ref. 10) felt that *S. aureus* had no role in the chafing form of diaper dermatitis. Leyden (Ref. 5) states that in diaper dermatitis colonization of dermatitic skin by *S. aureus* occurs frequently, and the more intense the inflammation, the more likely *S. aureus* colonization will occur. When *S. aureus* proliferates to high levels, secondary infection can be shown to occur. Weston, Lane, and Weston (Ref. 6) discussed the Leyden and Kligman study (Ref. 10) and stated that the role of colonization with *S. aureus* is not clear from that study. They noted that bacteriostatic agents, such as methylbenzethonium chloride, have been demonstrated in several studies to reduce the frequency of diaper rash. These authors concluded that, while quantitative increase in bacteria and bacterial products may possibly be involved in the genesis of diaper dermatitis, there is no firm proof that bacteria account for the dermatitis.

Pittillo et al. (Ref. 9) suggested that the inflammation that occurs in diaper rash tended to decrease the number of bacteria found in infants with diaper rash as compared to normal infants. Leyden, Marples, and Kligman (Ref. 12) have noted just the opposite with *S. aureus*, namely that *S. aureus* thrives better in inflamed skin, and that corticosteroids are effective therapy for atopic dermatitis with *S. aureus* involvement because suppression of inflammation leads to unfavorable conditions for *S. aureus*. Therefore, it is possible in the case of diaper rash that the accompanying inflammation inhibits the normal flora while it allows the overgrowth of potential pathogens that may cause secondary infections. Any antimicrobial treatment should counteract this shift, not intensify it. Also, as Leyden, Marples, and Kligman (Ref. 12) state, antibiotic therapy to treat infection in the diaper area should be limited to 1 week because prolonged antibiotic therapy may invite colonization with resistant organisms or new pathogens. Therefore, the agency has concerns about the safety and efficacy of simply using antimicrobials (antibacterials or antibiotics) in the diaper area just for the purpose of generally reducing the microflora count. The agency believes that regular use could even worsen the problem if the antimicrobial caused undesirable changes in the balance of bacteria in the skin flora.

The studies discussed above show that there are different theories on the role of bacteria in causing or aggravating diaper rash. It appears to be generally accepted that primary chafing (irritant) diaper dermatitis which results from friction and maceration of constantly wet skin (Refs. 2, 3, 5, and 10) is the most common type of diaper rash (Refs. 2, 4, 5, 6, and 10), the least serious (Ref. 10), and the type usually treated with OTC drugs (Ref. 10). The agency believes that this condition is best treated by changing diapers more frequently and by applying a skin protectant drug product for protection of the area from the irritant(s). Questions that remain to be answered are whether the presence of antimicrobial ingredients in OTC diaper rash drug products serves a useful function in treating this type of diaper rash and in preventing secondary infection and other complications that might occur. Based upon the available data, the agency classifies the use of topical antimicrobial ingredients and the claims mentioned above for OTC diaper rash drug products in Category III.

References

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

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

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

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(7) Brookes, D.B., R.M. Hubbert, and I. Sarkany, "Skin Flora of Infants with Napkin Rash," *The British Journal of Dermatology*, 85:250–253, 1971.

(8) Brown, C.P., R.M. Tyson, and F.H. Wilson, "Dermatitis (Diaper Rash): A Bacteriologic Study of the Diaper Region," *The Pennsylvania Medical Journal*, 55:755–758, 1952.

(9) Pittillo, R.F., et al., "Bacterial Flora of Infants, Skin: Comparison Between Diaper-Occluded and Unoccluded Areas," *International Journal of Dermatology*, 12:245–249, 1973.

(10) Leyden, J.J., and A.M. Kligman, "The Role of Microorganisms in Diaper Dermatitis," *Archives of Dermatology*, 114:56–59, 1978.

(11) Montes, L.F., et al., "Microbial Flora of Infant's Skin: Comparison of Types of Microorganisms Between Normal Skin and Diaper Dermatitis," *Archives of Dermatology*, 103:400–406, 1971.

(12) Leyden, J.J., R.R. Marples, and A. M. Kligman, "*Staphylococcus aureus* in the Lesions of Atopic Dermatitis," *British Journal of Dermatology*, 90:525–530, 1974.

2. Several submissions to the Antimicrobial I Panel (Ref. 1), the Antimicrobial II Panel (Ref. 2), and the Miscellaneous External Panel (Refs. 3 and 4) were for products containing antimicrobial active ingredients with labeling claims for ammoniacal diaper dermatitis such as "combats ammonia-forming bacteria that can be a major cause of diaper rash and odor," "eliminates cause of diaper rash (ammonia dermatitis)", and "aids in preventing the occurrence of ammoniacal dermatitis when used regularly." A number of the submissions (Refs. 2 and 3) included controlled clinical studies on a series of diaper rash products containing methylbenzethonium chloride in both topical drug products and products for impregnating diapers. One submission (Ref. 4) included clinical studies and in vitro data for a diaper rash cream containing benzethonium chloride. Several submissions (Ref. 1) included in vitro data on triclosan and on a triclosan-containing baby powder. These studies and data are discussed as part of the individual ingredient evaluations later in this document.

According to many of the submissions, ammonia is produced from urea in urine by the action of certain microorganisms; this ammonia causes ammoniacal diaper dermatitis; and antimicrobial agents such as methylbenzethonium chloride, benzethonium chloride, or triclosan, through their antibacterial activity, reduce the number of these microorganisms and thereby reduce the amount of ammonia produced. These submissions included published articles that discussed this condition, and the articles were generally based on Cooke's 1921 theory of ammoniacal dermatitis (Ref. 5). Cooke noted that ammonia was first implicated in the etiology of diaper dermatitis when Southworth (1913) and Zahorsky (1915) noted that a strong ammonia odor in diapers often accompanied the clinical disease. Cooke (Ref. 5) isolated urea-splitting bacteria which he found in the stool cultures of 31 infants and children, from age 1½ months to 4 years old, who had diaper dermatitis. He suggested the name *Bacillus ammoniagenes* for the organism which was later reclassified as *Brevibacterium ammoniagenes* (*B. ammoniagenes*). Cooke recognized that other organisms are capable of splitting urea to form ammonia—including *S. aureus*, *Sarcina lutea*, and *Bacillus proteus*—although he seldom found these other organisms in the stools examined in his study. Cooke applied *B. ammoniagenes* cultures with and without 1 percent urea to his arm under occlusion, and reported that erythema developed in the areas where the organisms and urea were applied, but there was no erythema in the areas where only the organisms were applied. Cooke concluded that the skin lesions were caused by the ammonia and not by the bacteria. Although Cooke did not attempt to reproduce the lesions experimentally on infants, he concluded that the evidence was sufficient to show that ordinary diaper rash is a dermatitis caused by ammonia being produced. Cooke concluded that the ammonia was produced by *B. ammoniagenes* that infest the diaper from the feces. He determined that, in the urine soaked diaper, this bacterium is able to decompose the urinary urea into free ammonia by the following reaction:

$$CO(NH_2)_2 + 2H_2O = (NH_4)_2CO_3 = 2NH_3 + H_2O + CO_2$$

Cooke stated that formation of ammonia from urea by bacteria must be

accomplished by the bacterial enzyme urease, but he was unable to extract urease. Cooke therefore concluded that the inhibition of the ammonia formation depended on the inhibition of bacterial growth rather than upon inhibition of urease activity. Cooke further suggested that "Since the dermatitis in these cases is a result of ammonia formed by bacterial action on urea in the diaper, it follows that the simplest and most logical method of prevention is to treat the diaper and not the infant." Cooke recommended the use of three nonvolatile antiseptics to impregnate the diaper in ammonia dermatitis: (i) A 1:5,000 solution of mercuric chloride, (ii) a 1:5,000 solution of mercuric iodide, and (iii) a 1:20 solution of boracic acid. In 1947, Benson et al. (Ref. 6), attempting to use a less toxic antiseptic than those Cooke recommended, impregnated diapers with a quaternary ammonium compound, namely para di-isobutyl-cresoxy-ethoxy-ethyl di-methyl benzyl ammonium chloride monohydrate, later named methylbenzethonium chloride.

The agency notes that Cooke's theory of ammoniacal dermatitis was originally well accepted, published in several text books (Refs. 7, 8, and 9), and went unchallenged until more recent studies raised questions regarding this theory. Later researchers such as Pratt (Ref. 10) described other rashes in the diaper area that were not related to the wearing of diapers. Weston, Lane, and Weston (Ref. 11) listed 23 other skin conditions occurring in the diaper area that required differential diagnosis from diaper-caused diaper rash. Furthermore, whereas Cooke had concluded that all diaper-caused rashes resulted from ammonia irritation, later researchers such as Burgoon, Urbach, and Grover (Ref. 12) began to suggest that diaper-caused dermatitis was not a single entity, but could result from several factors, such as (1) maceration and sweat retention from continuous contact with a wet diaper, especially when used with an impervious diaper cover, (2) primary irritation reaction from contact with feces, (3) allergic reactions to detergent soap preparations, and (4) mechanical irritation from the rubbing of a tight wet diaper. Finally, Leyden et al. (Ref. 13) concluded that ammonia liberated by the action of *B. ammoniagenes* was clearly not an important causative factor in diaper dermatitis and perhap not a factor at all.

Leyden et al. (Refs. 13 and 14) cultured squeezings from the morning diapers of 63 normal infants and 18 infants with a chafing, irritant type diaper dermatitis ("ammoniacal dermatitis," not candida infections or other dermatitis) and isolated a variety of organisms from all of the infants. The results showed that the presence of a strong ammonia-producing organism did not correlate with the presence of diaper dermatitis. Twelve (66.7 percent) of the 18 infants with diaper dermatitis had organisms capable of liberating ammonia in 24 hours, compared to 12 (19.0 percent) of the 63 infants free of any rash. However, strongly positive urea-splitting large colony diphtheroids capable of liberating ammonia in 4 to 6 hours, which the authors identified as similar to Cooke's *B. ammoniagenes*, were rarely recovered. Nevertheless, the *B. ammoniagenes* prevalence was five times as frequent in infants with diaper dermatitis (16.6 percent) than in normal infants (3.2 percent). Conversely, the total of strongly positive urea-splitting isolates capable of liberating ammonia in 4 to 6 hours was found to be slightly less in those infants with diaper rash (44.4 percent) than in normal infants (52.3 percent). Leyden (Ref. 14) concluded that neither the prevalence nor the density of urea-splitting organisms was significantly different for either population.

Leyden et al. (Ref. 13) also determined the ammonia levels, both free ammonia and total ammonia after incubation with urease, in the squeezings from the morning diapers of 82 normal infants and 26 infants with diaper rash. The mean total ammonia after incubation with urease was found to be slightly higher in the infants with diaper rash (7,803 parts per million (ppm)) than in the normal infants (7,556 ppm). Conversely, the level of free ammonia tended to be higher in the normal infants. The mean level of free ammonia in normal infants was 465 ppm and in infants with diaper dermatitis was 402 ppm. A total of 27 percent of the infants with diaper dermatitis had levels of free ammonia in excess of 500 ppm as compared to 22 percent of the normal infants. A total of 12 percent of infants with diaper rash and 22 percent of normals had a level of 600 ppm or greater. The authors concluded that there was no significant difference between the two groups.

Finally, Leyden et al. (Ref. 13) found that urine containing 1.6 percent ammonia (five times the mean of infants with diaper dermatitis) failed to produce diaper rash when placed on the skin of the buttocks of 10 infants under an occlusive dressing for 24 hours. Additional, more challenging skin studies were conducted on the arms of adult volunteers. Repeated application for 5 days of 1.6 percent ammoniated urine and 2.5 percent or 5 percent ammonium hydroxide also failed to induce damage on normal skin of 10 adults. However, repeated application of 10 percent ammonium hydroxide was able to produce erythema in 1 of 10 adult subjects after 48 hours of occlusion. Also, repeated applications (for 72 hours) of urine with both 0.5 percent and 0.05 percent ammonium hydroxide were able to produce erythema on scarified adult skin. Because 27 percent of the infants with diaper rash and 22 percent of the normal infants had a level of 0.05 percent or greater ammonia in their urine, Leyden et al. concluded that ammonia could possibly play a secondary role in aggravating already damaged skin, but that by itself it does not initiate a dermatitis. The authors state "In this light, we would regard measures aimed at acidifying urine, or the application of antimicrobial agents for the skin to diapers, as unsound and superfluous prophylactic practices."

Berg, Buckingham, and Stewart (Ref. 15) and Buckingham and Berg (Ref. 16) studied the roles of feces and urine, particularly ammonia, in the etiology of diaper dermatitis using the hairless mouse cutaneous primary irritation test and appeared to come to somewhat different conclusions than Leyden et al. (Ref. 13). For example, while noting that the work of Leyden et al. suggested that ammonia per se was not a primary factor in the induction of diaper dermatitis, these authors nevertheless stated that "While it is generally accepted that several etiologies are involved, the clear clinical association between the odor of ammonia on diapers and the presence of diaper dermatitis remains as strong today as it was at the turn of the century when ammonia was first assigned a role in this malady," (Ref. 15). In the study on the irritancy of infant urine, Berg, Buckingham, and Stewart (Ref. 15) found that "Infant urine did not cause skin irritation when patched on hairless mice for 48 hours, but skin damage did become apparent after continuous exposure for 10 days," and therefore concluded that "While the irritation potential of urine appears to be low, long-term exposure of skin to urine may lead to irritation." The authors concluded that because "diapered infants are almost constantly exposed to urine, it is reasonable to postulate a primary role for urine in the etiology of some cases of diaper dermatitis." Berg, Buckingham, and Stewart also found that when infant feces and urine were combined in a patch test, the irritancy was substantially higher than when either feces or urine were tested alone.

They determined that this synergistic irritancy was the result of the enzyme action of urease in the feces producing ammonia from urea in the urine, but noted that the increase in irritancy appeared to be a function of the increase in pH rather than an effect of ammonia per se. Therefore, while the authors did suggest that ammonia played an indirect role in diaper dermatitis involving an interaction between urine and feces, they concluded that the irritancy to the skin can be directly attributed to fecal enzymes, particularly proteases and lipases, that become more active and thus more damaging as the pH increases.

Based on the above findings, the agency is unable to determine whether Cooke's original theory of ammonia diaper rash has been completely refuted by Leyden et al. (Ref. 13) and Leyden (Ref. 14) or whether it has been confirmed by Berg, Buckingham, and Stewart (Ref. 15) and Buckingham and Berg (Ref. 16) with a slight revision to the effect that ammonia does not directly cause the dermatitis, but ammonia, being highly alkaline, changes the pH and activates other irritating substances in the urine and feces to cause the dermatitis.

The Berg, Buckingham, and Stewart study (Ref. 15) and the Buckingham and Berg study (Ref. 16) only pertained to patch testing of mice and may not be directly applicable to diapers used on babies. Also, the Leyden et al. diaper juice tests (Ref. 13) only pertained to ammonia levels in diaper squeezings and did not test for pH, proteases, or lipases. Accordingly, the agency is unable to conclude that urease-producing bacteria growing in urine-soaked diapers could not also cause the same chain reaction (bacteria-urease-urine-ammonia-high pH-activated toxic fecal enzyme-skin irritation) that Berg, Buckingham, and Stewart attribute to the same urease-producing bacteria growing in the intestine.

The agency believes that Cooke's ammonia theory of diaper rash, while perhaps not yet disproven, has been sufficiently questioned by these more recent studies and that the theory may not be as simple and straightforward as Cooke originally proposed. Furthermore, none of the data submitted by the comments is sufficient to answer the specific points raised by these newer studies. The agency has determined that the issues raised by the newer studies need further clarification and that there does not appear to be a generally recognized theory at this time to support OTC treatment or prevention of ordinary, mild diaper rash with antimicrobial drug products. Therefore, the agency is classifying in Category III those antimicrobial claims that are based upon the activity of diaper rash drug products against specific urea-splitting bacteria or are based upon proposed mechanisms of action such as Cooke's ammonia theory of diaper rash. Before claims of this type can be classified in Category I for antimicrobial-containing diaper rash drug products, further data are needed to demonstrate the effects, if any, of topical antimicrobials on the urea-splitting bacteria present in the microbial flora of infant skin in the diaper area. In addition, data are needed to show the amount of ammonia in the diaper, and whether any such changes in the amount of ammonia present correlate with changes in diaper dermatitis. Any claims concerning this ammonia theory need to be justified by clinical studies on infants that include bacteriological studies to correlate a reduction in ammonia-producing bacteria with a clinical improvement in the diaper rash.

Antimicrobial ingredients with claims for ammoniacal diaper dermatitis have been evaluated in the discussions of the ingredients benzethonium chloride, methylbenzethonium chloride, and triclosan. (See comments 6, 11, and 16 below.) Diaper rash products used to impregnate diapers with antimicrobial ingredients are also discussed below. (See comment 4 below.)

References

(1) OTC Volumes 020077, 020078, and 020079.

(2) OTC Volumes 070074, 070075, 070076, 070078, 070079, 070080, and 070081.

(3) OTC Volumes 160242, 160243, 160244, 160245, 160246, 160247, and 160427.

(4) OTC Volume 160042.

(5) Cooke, J.V., "Etiology and Treatment of Ammonia Dermatitis of the Gluteal Region of Infants," *American Journal of Diseases of Children*, 22:481–492, 1921.

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(16) Buckingham, K.W., and R.W. Berg, "Etiologic Factors in Diaper Dermatitis: The Role of Feces," *Pediatric Dermatology*, 3:107–112, 1986.

3. One comment stated that active ingredients that are not classified as skin protectants, when used in diaper rash drug products, should have a record of safety especially with regard to use on infants' skin.

The agency agrees with the comment that ingredients used in OTC diaper rash drug products should have a proven safety record with regard to use on infants' skin, especially when used for prolonged periods of time and under occlusion. Safety is a particular concern with topical antimicrobial ingredients because of serious or even fatal poisoning which may result from transcutaneous absorption. Reports have shown that mercury, phenol, resorcin, boric acid, and hexachlorophene can be very toxic and cause death in infants, even when applied externally (Ref. 1). Even drugs considered safe for use in adults may be of concern when used on infants because, as Barnett (Ref. 2) pointed out, the skin of infants differs in many fundamental respects from that of adults. Because infant skin is just half as thick as adult skin (Ref. 3), and because of the high surface-to-volume ratio and the peculiarities of systemic metabolism and detoxification in very young children, the risk of systemic effects from topical preparations is increased (Ref. 4). Major differences exist in drug disposition between pediatric and adult patients, and a number of enzyme systems are deficient or even absent in the neonate (Ref. 5). For example, immaturity of the enzyme hepatic glucuronyl transferase results in diminished conjugation of chloramphenicol to form the inactive acid glucuronide (Ref. 5). Another antibiotic (novobiocin) directly inhibits hepatic glucuronyl transferase in neonates, resulting in an accumulation of metabolic products toxic to the baby (Ref. 5).

The Antimicrobial I Panel, in its advance notice of proposed rulemaking for OTC topical antimicrobial drug

products (September 13, 1974; 39 FR 33103), recommended warnings against the use of several antimicrobial ingredients on infants under 6 months of age until additional studies were submitted to demonstrate safety in animals deficient in these detoxification mechanisms. These ingredients included triclocarban, cloflucarban, triclosan, phenol, and chloroxylenol, all of which are metabolized and eliminated from the body by glucuronide or sulfate conjugation in the liver. As stated in the tentative final monograph for OTC topical antimicrobial drug products (January 6, 1978; 43 FR 1210), the agency concurs with these recommended warnings and further believes that products marketed with diaper rash claims should be safe for use on infants of all ages.

Diaper rash drug products are used on an area of the body and under conditions that favor percutaneous absorption and increased susceptibility of the skin to irritants. The inguinal region, urorectal area, scrotum, and female genitalia are sites of application with enhanced percutaneous absorption (Refs. 6 and 7). Diseased or damaged skin may also result in the loss of barrier function of the stratum corneum and increase percutaneous absorption (Refs. 6 and 7). The increased temperature and moisture that are produced by the occlusion of a diaper, rubber pants, or clothing will enhance skin permeability and percutaneous absorption (Refs. 8, 9, and 10). Continuous exposure to urine also increases permeability of skin, suggesting that infant skin in the diaper area may become more permeable to ingredients that might be present in the diaper environment (Ref. 9). Wester and Maibach (Refs. 6 and 7) state that when some or all of these parameters are involved, absorption from topical administration is enhanced. The hydration and maceration of skin that is promoted by the semioccluded diaper environment is also known to increase the susceptibility of the skin to many irritants (Ref. 11). Further, infants may become sensitized to regular use of topically applied antibacterial agents which may result in inflammation or allergic contact dermatitis that may aggravate or even induce a rash (Refs. 3, 4, and 12). Thus, an evaluation of each component in diaper rash drug products for sensitization and irritation potential is necessary.

Current agency regulations in 21 CFR 369.20 contain recommended warnings against use on large areas of the body for several OTC topical antimicrobial drugs, i.e., boric acid, carbolic acid (phenol), cresols, and mercury preparations. Because diaper rash drug products are applied over a relatively large percent of the surface area of an infant's body, products containing these antimicrobials would not be appropriate for treating or preventing diaper rash.

For antimicrobial ingredients to be placed in Category I for use on infants in OTC diaper rash drug products, adequate data demonstrating safety addressing the concerns raised in this document, as well as adequate efficacy data, are needed. Discussion of the safety of individual antimicrobial ingredients considered in this rulemaking appears in Part I comments 5 to 19 below.

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4. One company submitted information on three types (tablets, granules, and concentrated solution) of laundry products containing methylbenzethonium chloride to be dissolved in water for use as a final rinse to impregnate diapers. These products were labeled with the claim "eliminates cause of diaper rash (ammonia dermatitis)" (Ref. 1). Another company submitted information on a general disinfectant product containing benzalkonium chloride with directions to dilute for use as a "final sanitizing diaper rinse" (Ref. 2). However, the product did not bear any specific claims about diaper rash. Another company submitted information on moist disposable towelettes impregnated with benzalkonium chloride and labeled for use to clean the baby when changing diapers to help "alleviate baby's minor diaper irritations," (Ref. 3).

The agency notes that laundry products with antimicrobial claims are regulated as disinfectants by the Environmental Protection Agency (EPA), which has the following policy: An EPA-registered rinse for diapers may only claim to control, on the treated diaper, the microorganism that causes diaper rash (Ref. 4). FDA has jurisdiction over products used on humans. Therefore, depending on the label claims, laundry products regulated by EPA may also be regulated under the Federal Food, Drug, and Cosmetic Act (the act) as drug products.

In determining whether a product is a drug, FDA considers the properties of the product, its intended uses, and the definition of the term "drug" in the act. Diaper rinses intended for use in the prevention or treatment of diaper rash are drugs within the meaning of section 201(g) of the act [21 U.S.C. 321(g)]. The term "drug" is defined in section 201(g)(1) as, among other things, "* * * articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease * * * and * * * articles (other than food) intended to affect the structure or any function of the body * * *." A drug generally is a chemical or a combination of chemicals in liquid, paste, powder, or other drug dosage form that is ingested, injected, or instilled into body orifices, or rubbed or poured onto the body in order to achieve its intended medical purpose.

A diaper rinse is a chemical entity or a combination of chemical entities intended for in vivo use. An article which is a drug within the meaning of section 201(g) of the act does not lose its status as a drug merely because its directions for use recommend application by means of a household article such as a cotton ball or swab, or, in this case, an infant's diaper. In fact, a

unique method of delivery of a drug product may cause the article to be a "new drug" under the meaning of section 505 of the act (21 U.S.C. 355) if the dosage form is not one that is generally recognized as safe and effective for this use.

Based upon the above, the agency has the following comments on the specific products that were submitted. The three diaper rinse products containing methylbenzethonium chloride (Ref. 1) are drugs based upon their intended use as expressed in the labeling statements: "Eliminates cause of diaper rash (ammonia dermatitis)," "* * * diaper rash (ammonia dermatitis) is due to irritating ammonia released by the bacterial decomposition of the baby's urine," "* * * eliminates the cause of diaper rash by checking formation of urinary ammonia in wet diapers * * *," "Use only as a final, clean rinse," "* * * methylbenzethonium chloride that fights the bacteria that cause ammonia to form * * *." The active principle in these products is the chemical methylbenzethonium chloride. Its mode of action is further delineated under the section entitled Efficacy Evaluation in the company's submission (Ref. 1), which states in part:

> * * * methylbenzethonium chloride, released from ointment, cream and powder bases or from impregnated diapers, can effectively and safely ameliorate and prevent certain forms of diaper rash and does so presumably by killing microorganisms in urine and feces that produce ammonia and other (as yet, unspecified) irritating agents.

The agency does not, however, consider the product containing benzalkonium chloride (Ref. 2) to be a drug within the meaning of section 201(g) of the act as far as its intended use can be determined from the labeling or other submitted material. Although the product's label declares the active ingredient as alkyl dimethybenzylammonium chlorides (benzalkonium chloride), and the labeling directions recommend the product "For final sanitizing diaper rinse * * *" there is no indication in the product's labeling that it is intended to prevent or to treat diaper rash. It appears from the product's labeling and other backgound information that the product is intended solely for the disinfection or sanitization of inanimate objects, including diapers, and not for the treatment of a disease or condition.

The agency considers the baby wipe towelettes containing benzalkonium chloride (Ref. 3) to be a drug within the meaning of section 201(g) of the act because of the statement in its labeling: "helps alleviate baby's minor diaper irritations * * *." Moreover, the manufacturer's submission included a controlled clinical study to evaluate the effectiveness of using these baby wipe towelettes for diaper rash among other conditions and the study was specifically cited and discussed in the efficacy summary in the submission (Ref. 3). The manufacturer's action supports the position that the article is a drug intended for use in the treatment of diaper rash. The product's efficacy is apparently based upon the antimicrobial activity of benzalkonium chloride in the formulation. The agency's evaluation of this clinical study is discussed under comment 5 below.

References

(1) OTC Volumes 070078, 070079, 160242, 160247, and 160427.

(2) OTC Volume 020016.

(3) OTC Volume 020051.

(4) Letter from J. H. Lee, EPA, to C. J. Baker, Albright and Wilson, Inc., dated October 30, 1986, in OTC Volume 02DTFM, Docket No. 75N-183D, Dockets Management Branch.

B. Comments on Benzalkonium Chloride.

5. As noted in comment 4 above, two manufacturers submitted information (Refs. 1 and 2) on products containing benzalkonium chloride.

Benzalkonium chloride has been reviewed for safety for topical use in four other OTC drug rulemakings. In the advance notice of proposed rulemaking for OTC topical antimicrobial drug products (September 13, 1974; 39 FR 33103), the Antimicrobial I Panel concluded that this ingredient and two other quaternary ammonium compounds at a concentration of 1:750 (0.13 percent) could be regarded as safe as a skin wound cleanser provided that the product is not used repeatedly, covered with occlusive bandaging, or used in deep or extensive wounds (39 FR 33116). However, the Panel concluded that further toxicity data characterized by the absorption and systemic toxicity in a rodent and nonrodent species should be generated prior to the placement of these quaternary ammonium compounds into Category I for use other than as a skin wound cleanser (39 FR 33132). In the tentative final monograph for OTC topical antimicrobial drug products (January 6, 1978; 43 FR 1210), the agency did not include recommendations for further animal studies and stated that the systemic toxicity of quaternary ammonium compounds in animals is low and is indicative of and reflects the surfactant nature of the molecule (43 FR 1236). The agency stated that even though specific absorption and systemic levels in humans have not been reported for the three quaternary ammonium compounds reviewed, considering the concentrations applied, and extrapolating from animal studies, toxic effects at use levels would be unlikely (43 FR 1237). However, both the Panel (39 FR 33132) and the agency (43 FR 1237) noted that there are many reports on the irritating nature of the quaternary ammonium compounds on the skin, mucous membranes, and the eye and that the degree of irritation increases when quaternary ammonium compounds are used under occlusion.

In the advance notice of proposed rulemaking for OTC oral health care drug products (May 25, 1982; 47 FR 22760), the Advisory Review Panel on OTC Oral Cavity Drug Products (Oral Cavity Panel) concluded that benzalkonium chloride is safe as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used at concentrations of 0.01 to 0.02 percent. However, for children under 3 years of age the Panel did not recommend a dosage except under the advice and supervision of a dentist or physician.

In the advance notice of proposed rulemaking for OTC vaginal drug products (October 13, 1983; 48 FR 46694), the Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products (Vaginal Panel) concluded that data are insufficient to prove that benzalkonium chloride is safe for the relief of minor vaginal irritations. The Panel noted that toxicologically the quaternaries appear to be relatively safe when used in dilute solution and without occlusive dressing (48 FR 46717 to 46718). However, the Panel expressed concern that the relative ineffectiveness of quaternaries as bactericidal agents raise significant concern as to their safety for use in vaginal products because of the possibility of overgrowth of pathogenic organisms.

Benzalkonium chloride was also reviewed by the Advisory Review Panel on OTC Miscellaneous External Drug Products (Miscellaneous External Panel) in the advance notice of proposed rulemaking for OTC drug products for the control of dandruff, seborrheic dermatitis, and psoriasis (December 3, 1982; 47 FR 54646). The Panel concluded that benzalkonium chloride is safe for OTC use for controlling dandruff in concentrations of 0.05 to 0.2 percent (47 FR 54671).

Animal safety data for benzalkonium chloride included a 1-year feeding study in dogs (Refs. 3 and 4) and a 12-week feeding study in rats (Refs. 3 and 5). In addition, 2-year rat feeding studies were cited (Refs. 1 and 3). One report (Ref. 6) attempted to calculate the long-term safety factor in humans from use of

eating utensils sanitized with benzalkonium chloride and concluded that there was a rather wide margin of safety of 833 to nearly 7,000 times.

Pfeffer and Smith (Ref. 7) reported a skin test that involved application of a 2-inch square gauze patch moistened with a 1:1,000 dilution of benzalkonium chloride to the backs of 100 infants aged 1 day to 2 years. The patch was left in contact with the skin for 24 hours. No reactions of any kind were noted either at the end of the 24-hour period or after 48 hours. The authors also reported that no irritation was noted in any of the 154 patients on whom benzalkonium chloride-rinsed diapers were used therapeutically or prophylactically (Ref. 7). (These studies are discussed below.)

The manufacturer of the disposable towelettes impregnated with a lotion containing benzalkonium chloride submitted two studies on the finished product to show that it did not irritate the skin. The manufacturer noted that the lotion product was formulated to contain 0.02 percent benzalkonium chloride by weight, but that the amount of ingredient expressed from the paper towelette is 0.015 percent because the balance is irreversibly adsorbed on the paper. In one study (Ref. 8), 100 females were subjected to prophetic patch tests. Towelettes were cut in quarters, folded, and applied to the back and covered with a sheer occlusive patch. This patch was then reinforced with ½-inch-waterproof tape to assure good contact and allow the square perforated area to breathe. The material remained in contact with the skin for 48 hours. Upon removal of the patches, the test areas were observed at once for immediate reaction. A final examination for delayed reactions was made 72 hours after application. Retests were done 14 days later. The reported results were that there was no evidence of any primary irritation on the initial 48-hour patch test and no indication of sensitization of the skin on the retest performed 14 days later. However, the agency notes that because the perforated area of the patch was allowed to breathe, the results may not be reflective of irritation that may develop in an occluded diaper area.

In the second study, a clinical test was conducted for 4 weeks on over 100 infants on which impregnated towelettes were used to cleanse the hands, face, and diaper area (Ref. 9). A consulting dermatologist examined the infants at the start of the study, at week two, and at week four and found no adverse reactions to the use of the tested product.

The agency finds the above studies show that the skin irritation potential of benzalkonium chloride when used under occlusion for a short term does not appear to be a problem. However, the agency is not able to reach any conclusions about the sensitizing potential of the ingredient under the occlusive conditions found in the diaper area when this ingredient is used chronically on infants and children. The agency has determined that additional data are needed to demonstrate the safety of benzalkonium chloride or other quaternary ammonium compounds for use in diaper rash drug products for chronic use on infants and children. Studies need to be done to determine the degree of absorption from broken skin (as evidenced by blood levels) and the relationship between these blood levels and the blood concentration that produces no adverse effect in animals. In addition, studies are needed to determine the skin irritation and sensitization potential in infants when the ingredient is applied chronically under occlusion as occurs in the diaper area.

Several studies involved the antibacterial activity of fabric impregnated with benzalkonium chloride (Refs. 7, 10, and 11). Latlief et al. (Ref. 11) studied the antimicrobial activity of five quaternary ammonium compounds, including benzalkonium chloride, used to impregnate cotton fabric to prevent ammonia formation from urea by *Proteus mirabilis* (*P. mirabilis*). Benzalkonium chloride applied by exposing the fabric for 10 minutes at 45 °C was capable of inhibiting ammonia production for 16 hours at a 1:25,000 dilution, for 24 hours at a 1:3,000 dilution, and up to 7 days at a 1:1,000 dilution. All controls became positive in 10 hours, hence, the 16- and 24-hour readings represent a 6- and 14-hour delay in ammonia production.

Pfeffer and Smith (Ref. 7) conducted in vitro bacteriologic studies on the antibacterial activity of dilutions of benzalkonium chloride against a proteus with known urea-splitting activity and a saline suspension of normal infant stool as the test inoculum. They concluded that a 1:5,000 dilution of a disinfectant solution containing 10 percent benzalkonium chloride would inhibit ammonia formation in the diaper. In the discussion of Cooke's ammonia theory of diaper rash (see comment 2 above), the agency noted that this theory has been questioned by more recent studies. As discussed in comment 2 above, the agency has determined that any claims concerning this ammonia theory need to be justified by clinical studies on infants that include bacteriological studies to correlate a reduction in ammonia-producing bacteria with a clinical improvement in the diaper rash. Therefore, the agency does not find in vitro tests alone to be sufficient to prove effectiveness for products used for ammonia-caused diaper rash.

Pfeffer and Smith (Ref. 7) also conducted two clinical trials to prevent or treat diaper rash. In one study to prevent diaper rash, a group of 90 incontinent nonambulatory infants and children in 4 wards in a state mental institution were evaluated for 3 months. The diapers used were cleaned by commercial laundry methods that were the same for each of the 4 wards, except that benzalkonium chloride was used in the final rinse for the diapers used in 2 wards. Thus, the other two wards served as a control. Examinations of the patients in both test and control groups were made twice weekly, but no significant changes in the existing lesions were noted in either group over the 3-month period.

The treatment study was an uncontrolled study in which 64 infants with diaper rash used diapers impregnated with benzalkonium chloride in a 1:5,000 dilution (1 teaspoonful of 10 percent product diluted in 2 quarts of tap water). The infants' mothers were instructed not to use any other medication, such as antiseptic powders, ointments, or diaper rinses. The results in 62 of the 64 cases were good with the time for clearing depending on the severity of the lesions present. All 19 mild and 25 of the 28 moderate cases cleared within 1 week. Two moderate cases cleared after 2 weeks and one failed to respond. Chronic, severe rashes began to improve within a few days and inflammatory changes were gone within 2 weeks. One severe case did not respond. The authors concluded that benzalkonium-chloride impregnated diapers were effective in curing ammoniacal diaper dermatitis in 62 out of 64 cases and under usual circumstances would be equally effective for the prophylaxis of this condition. However, this was an uncontrolled study, and the agency does not consider it adequate to demonstrate effectiveness.

Kantor, Botwinick, and Botwinick reported a controlled clinical study that evaluated the effectiveness of using disposable towelettes moistened with benzalkonium chloride for diaper rash (Ref. 9). Diaper rash was described as a "Condition of the skin occurring in the groin and buttocks as well as in the folds, associated with wetness, warmth, and friction rather than caused by the diaper material itself. It is manifested by redness, pustules, erosion, etc." During the 4-week study, the incidence of

diaper rash was noted at the start of the study and at 2 and 4 weeks. A group of 102 infants was treated with the benzalkonium chloride towelettes in addition to their usual cleansing regimen; 25 percent improved, 64 percent remained the same, and 11 percent became worse. Of the control group of 98 infants who used their usual cleansing regimen only, 18 percent improved, 56 percent stayed the same, and 26 percent became worse. The authors concluded that the treated group was significantly better than the control group and that the treated group had a less dry or scaly diaper area than the control group. However, the agency notes that this study was not adequately controlled. For example, instead of comparing the benzalkonium-chloride impregnated disposable towelettes with disposable towelettes moistened only with the (alcohol) vehicle as the control, the control group was not provided any sort of disposable towelettes but was instructed to follow its individual cleansing regimen. Thus, the cleansing regimen was not comparable between the treatment and control groups. These groups also differed in other ways, e.g., the number that used cloth diapers or disposable diapers and the number of diapers used daily. Finally, bacteriological studies were not done on the infants. Therefore, while this study indicates that benzalkonium chloride may be beneficial for treating diaper rash, additional data from properly controlled studies are needed before this ingredient can be classified as Category I for effectiveness. The agency believes that in vivo bacteriological studies are needed; specifically in vivo studies in infants to demonstrate the effect of the antibacterial activity of benzalkonium chloride on the skin flora and whether this effect correlates with clinical improvements in the diaper rash. Also bacteriological studies are needed to show that the long-term use of benzalkonium chloride does not result in potentially harmful changes in the normal flora of the skin in the diaper area. Based upon the above discussion, the agency is classifying benzalkonium chloride for use in diaper rash drug products in Category III for both safety and effectiveness.

References

(1) OTC Volume 020016.

(2) OTC Volume 020051.

(3) Coulston, F., et al., "Toxicology of Benzalkonium Chloride Given Orally in Milk or Water to Rats and Dogs," *Toxicology and Applied Pharmacology*, 3:584–594, 1961.

(4) Coulston, F., and P. Garvin, "TS–19, Roccal, Germicide, One-Year Chronic Toxicity in Dogs: A Comparison of the Toxicity of Roccal in Combination with Milk and with Water," unpublished report in OTC Volume 020016.

(5) Coulston, F., and P. Garvin, "TS–19, Roccal, Germicide, A Comparison of the Toxicity of Roccol in Combination with Milk and with Water when Administered Orally to Male Albino Rats for Three Months," unpublished report in OTC Volume 020016.

(6) Drobeck, H.P., "Evaluation of Safety Factor for Roccal Residue on Eating Utensils," unpublished report in OTC Volume 020016.

(7) Pfeffer, W., Jr., and C.A. Smith, "A Note on the Treatment of Diaper Rash with Alkyl-Dimethyl-Benzyl-Ammonium Chlorides (Roccal)," *The Journal of Pediatrics*, 37:351–356, 1950.

(8) Blau, S., and N. Kanof, "Sample #7775 Washkins for Babies," unpublished report in OTC Volume 020051.

(9) Kantor, I.I., C.G. Botwinick, and I.S. Botwinick, "Wash'n Dry Baby Care Towelette Study," unpublished study in OTC Volume 020051.

(10) Propst, H.D., "The Effect of Bactericidal Agents on the Sterility of Surgical Linen: An Experimental and Clinical Study," *American Journal of Surgery*, 86:301–308, 1953.

(11) Latlief, M.A., et al., "Bacteriostatic, Germicidal, and Sanitizing Action of Quaternary Ammonium Compounds on Textiles: Prevention of Ammonia Formation from Urea by *Proteus mirabilis*," *The Journal of Pediatrics* 39:730–737, 1951.

C. Comment on Benzethonium Chloride

6. One manufacturer submitted data (Ref. 1) to the Miscellaneous External Panel for a diaper rash cream product containing a combination of benzethonium chloride, talc, dl-methionine, cysteine hydrochloride, and protein hydrolysate containing the amino acids 1-leucine, 1-isoleucine, 1-methionine, 1-phenylalanine, and 1-tyrosine. The labeling states that the product is for the treatment of, and as an aid in the prevention of, diaper rash, cradle cap, excoriations and chafing of the infant skin and that it "contains a germicide to help prevent irritation." The submission included studies on the use of the finished product in the treatment of ammonia dermatitis (diaper rash) and in vitro data on benzethonium chloride in prevention of ammonia formation from urea by *P. mirabilis*.

Elsewhere in this issue of the **Federal Register**, the agency states its tentative conclusions on the use of skin protectant ingredients for the treatment and prevention of diaper rash. The ingredients referred to by the comment, with the exception of benzethonium chloride, are addressed in that rulemaking. The use of benzethonium chloride in the treatment or prevention of diaper rash is addressed here.

Benzethonium chloride has been reviewed for safety for topical use in five other OTC drug rulemakings. In the advance notice of proposed rulemaking for OTC topical antimicrobial drug products (September 13, 1974; 39 FR 33103), the Antimicrobial I Panel concluded that this ingredient and two other quaternary ammonium compounds at a concentration not greater than 1:750 (0.13 percent) could be regarded as safe as a skin wound cleanser provided that the product is not used repeatedly, covered with occlusive bandaging, or used in deep or extensive wounds (39 FR 33116). However, that Panel concluded that further toxicity data, characterized by the absorption and systemic toxicity in a rodent and nonrodent species, should be generated prior to the placement of these quaternary ammonium compounds into Category I for use other than as a skin wound cleanser (39 FR 33132). In the tentative final monograph for OTC topical antimicrobial drug products (January 6, 1978; 43 FR 1210), the agency did not include recommendations for further animal studies and stated that the systemic toxicity of quaternary ammonium compounds in animals is low and is indicative of and reflects the surfactant nature of the molecule (43 FR 1236). The agency stated that even though specific absorption and systemic levels in humans have not been reported for the three quaternary ammonium compounds reviewed, considering the concentrations applied, and extrapolating from animal studies, toxic effects at use levels would be unlikely (43 FR 1237). However, both the Panel (39 FR 33132) and the agency (43 FR 1237) noted that there are many reports on the irritating nature of the quaternary ammonium compounds on the skin, mucous membranes, and the eye and that the degree of irritation increases when quaternary ammonium compounds are used under occlusion.

In the advance notice of proposed rulemaking for OTC antifungal drug products (March 23, 1982; 47 FR 12480), the Antimicrobial II Panel concluded that there are insufficient data available to permit final classification of the safety of benzethonium chloride for use in the treatment of athletes foot, jock itch, and ringworm. The Panel reviewed safety data in animals but noted that absorption from broken skin is unknown. The Panel recommended that studies be done to determine the degree of absorption of benzethonium chloride from broken skin, as evidenced by blood levels, and the relationship between these blood levels and the blood levels that produced no adverse effects in animals (47 FR 12527).

In the advance notice of proposed rulemaking for OTC oral health care

drug products (May 25, 1982; 47 FR 22760), the Oral Cavity Panel expressed concern about the safety of benzethonium chloride for long-term use on a daily basis in mouth rinses or gargles (47 FR 22860). The Panel was concerned that, although the salts of quaternary nitrogenous compounds are normally not lipophilic and not ionized, and are, therefore, poorly absorbed through the mucous membranes, the introduction of a highly lipophilic radical into the structure of benzethonium chloride might increase the lipid solubility and thus enhance penetration of this compound through the mucous membranes. The Panel feared that this would increase systemic absorption and therefore increase the possibility that toxic doses could be absorbed through the mucous membranes of the mouth and throat. The Panel stated that adequate data on absorption and attainment of toxic blood levels and the metabolic fate of the quaternary ammonia compounds are not available. It also stated that data on cumulative effects, including mutagenic, tumorigenic, or teratogenic effects, from continued daily use over a prolonged period of time in a mouthwash or gargle are not available. The agency finds that the use of benzethonium chloride on the mucous membranes in the diaper area for an extended period of time raises similar concerns.

In the advance notice of proposed rulemaking for OTC vaginal drug products (October 13, 1983; 48 FR 46694), the Vaginal Panel concluded that data are insufficient to prove that benzethonium chloride is safe for the relief of minor vaginal irritations. The Panel noted that toxicologically the quaternaries appear to be relatively safe when used in dilute solution and without occlusive dressing (48 FR 46717 to 46718). However, the Panel added that the relative ineffectiveness of quaternaries as bactericidal agents raises significant concern as to their safety for use in vaginal products because of the possibility of overgrowth of pathogenic organisms.

OTC topical use of benzethonium chloride for controlling cradle cap was reviewed by the Miscellaneous External Panel in the advance notice of proposed rulemaking for OTC drug products for the control of dandruff, seborrheic dermatitis, and psoriasis (December 3, 1982; 47 FR 54646). That Panel evaluated the same submission as identified above (Ref. 1). Although no data were submitted on the product's use in the control of cradle cap, the Panel concluded that the data related to the product's use in treating diaper rash showed that no irritation or sensitization was observed in any of the infants (Ref. 2). The Panel also noted that, as a preliminary to the study, the finished product was applied to the arms and forearms of 25 children and 25 infants for up to 4 hours in some cases. No irritation or other side effects were noted. The Panel concluded that benzethonium chloride is safe for OTC use in controlling cradle cap (47 FR 54671).

Although one panel has recommended that benzethonium chloride is safe for use in treating cradle cap, it does not necessarily follow that the ingredient is also safe for treating diaper rash. Other panels have raised concern about repeated use and use under an occlusive dressing. When used for treating and/or preventing diaper rash, the product is likely to be used for a long period of time, possibly over a large area and on more sensitive skin, and will be used under occlusion, i.e., diapers. The agency notes that, in the irritation test by Susca and Geuting (Ref. 2), the authors do 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 reach any conclusions about the sensitizing potential of the ingredient under the occlusive conditions found in the diaper area when this ingredient is used chronically on infants and children. The agency has determined that additional data are needed to demonstrate the safety of benzethonium chloride or other quaternary ammonium compounds for use in diaper rash drug products for chronic use on infants and children. Studies need to be done to determine the degree of absorption from broken skin (as evidenced by blood levels) and the relationship between these blood levels and the blood concentration that produces no adverse effect in animals. In addition, studies are needed to determine the skin irritation and sensitization potential in infants when the ingredient is applied chronically under occlusion as occurs in the diaper area.

Two clinical studies (Refs. 2 and 3) were conducted on the finished product compared with a placebo cream with no active ingredients. Because the finished product used in the studies contained other active ingredients in addition to benzethonium chloride, the contribution of benzethonium chloride alone cannot be determined. Also, both studies lacked sufficient details to be considered adequately controlled clinical trials. (For a discussion of these studies, see the agency s conclusions on the use of skin protectant drugs for diaper rash, elsewhere in this issue of the **Federal Register**.)

The submission included articles from the literature to demonstrate effectiveness (Refs. 4 and 5) and a report by Latlief et al. (Ref. 6) on the antimicrobial activity of five quaternary ammonium compounds, including benzethonium chloride, used to impregnate cotton fabric to prevent ammonia formation from urea by *P. mirabilis*. In the discussion of Cooke's ammonia theory on diaper rash (see comment 2 above), the agency noted that this theory has been questioned by more recent studies. As discussed in comment 2 above, any claims concerning this ammonia theory need to be justified by clinical studies on infants that include bacteriological studies to correlate a reduction in ammonia-producing bacteria with a clinical improvement in the diaper rash. Therefore, the agency does not find in vitro tests alone to be sufficient to prove effectiveness for ammonia-caused diaper rash.

The agency believes that in vivo bacteriological studies are needed; specifically in vivo studies in infants to demonstrate the effect of the antibacterial activity of benzethonium chloride on the skin flora and whether this effect correlates with clinical improvements in the diaper rash. Also bacteriological studies are needed to show that the long-term use of benzethonium chloride does not result in potentially harmful changes in the normal flora of the skin in the diaper area.

Based upon the above discussion, the agency is classifying benzethonium chloride for use in diaper rash drug products in Category III for both safety and effectiveness.

References

(1) OTC Volume 160042.

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

(3) Christian, J.R., and F. Gonzalez, "Topical Treatment of Acute and Chronic Diaper Rash with Amino Acid Creme," *Clinical Medicine*, 8:225–231, 1961.

(4) Lawrence, C.A., "Quaternary Ammonium Surface-Active Disinfectants," in "Disinfection, Sterilization and Preservation," edited by C.A. Lawrence and S.S. Block, Lea and Febiger Publishing Co., Philadelphia, pp. 430–452, 1968.

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D. Comment on Boric Acid

7. One comment noted that boric acid and other borates were used in OTC topical antimicrobial drug products for the treatment of diaper rash, and that boric acid was listed as an ingredient in marketed products submitted to the Panel (47 FR 39408). The comment stated that its review of the OTC volumes cited at 47 FR 39409 showed that boric acid was an ingredient in two diaper rash powder products, one ointment, and one cream at concentrations ranging from 0.5 to 7.5 percent, and that the boric acid was used as a buffer to react with ammonia. The comment also referred to its comments to the other rulemakings (external analgesic, antifungal, and skin protectant) for diaper rash drug products.

The agency has reviewed the references referred to by the comment (Refs. 1 through 4) and notes that the products contain boric acid at concentrations of 0.5, 3, 4.55, and 7.14 percent. However, the product containing 0.5 percent did not have a labeling claim for diaper rash. Although the comment stated that boric acid was used as a buffer to react with ammonia, which implies that it was an inactive ingredient, the labeling of two products (Refs. 1 and 2), and information in the data submitted for the third product (Ref. 4) list boric acid as an active ingredient.

In evaluating the current formulations of these products, the agency has determined that the three products with diaper rash claims have been reformulated to delete the boric acid (Refs. 5, 6, and 7). 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. 8). The manufacturer has not submitted any data on this product to the OTC drug review.

The Miscellaneous External Panel stated that antimicrobial products to control bacteria may prevent further skin irritation associated with diaper rash (47 FR 39406 at 39409). The Panel did not review or categorize ingredients for use in diaper rash drug products, but recommended that those ingredients be referred to appropriate rulemakings. Although boric acid was not classified by the Antimicrobial I Panel, the Antimicrobial II Panel classified it in Category II for acne use and in Category III for antifungal use in athletes foot, jock itch, and ringworm. The Antimicrobial II Panel said it was safe at concentrations of 5 percent or less, but there were no data available to evaluate the effectiveness of boric acid for acne and antifungal uses.

A number of other 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. Therefore, based on these panels' recommendations and the available data, the agency considers boric acid to be Category II for safety as a topical antimicrobial active ingredient in diaper rash drug products.

The comments to the other rulemakings for OTC diaper rash drug products requested that boric acid be considered as an inactive ingredient in those products. These comments are addressed elsewhere in this issue of the **Federal Register**.

References

(1) OTC Volume 160040.
(2) OTC Volume 160077.
(3) OTC Volume 160091.
(4) OTC Volume 160236.
(5) Comment No. RPT005, Docket No. 75N–0183, Dockets Management Branch.
(6) Letter from J.A. Devaney, The Mentholatum Company, Inc., to L. Geismar, FDA, dated October 23, 1986, in OTC Volume 02DTFM, Docket No. 75N–183D, Dockets Management Branch.
(7) Comment Nos. C00163 and LET083, Docket No. 75N–0183, Dockets Management Branch.
(8) Smith, G.H., "Diaper Rash and Prickly Heat Products," *in* "Handbook of Nonprescription Drugs," 8th Ed., American Pharmaceutical Association, Washington, p. 651, 1986.

E. Comment on Calcium Undecylenate

8. One manufacturer submitted data for two diaper rash products (an ointment and a powder) containing 15 percent calcium undecylenate to the Miscellaneous External Panel (Ref. 1) and the Antimicrobial I Panel (Ref. 2). The information submitted indicated that the powder product also contained 3 percent boric acid as an active ingredient. A subsequent submission by the same manufacturer (Ref. 3) stated that both products had been reformulated, i.e., the boric acid was deleted from the powder product and the calcium undecylenate was deleted from the ointment product. Thus, the ointment product no longer contains an antimicrobial active ingredient. The current labeling (Ref. 4) for the reformulated baby powder product, which now contains 10 percent calcium undecylenate in talc (Ref. 3), in part reads "helps heal, relieve, and prevent diaper rash, prickly heat, and chafing," and "medicated with calcium undecylenate to kill harmful bacteria and fungi while forming a protective barrier that repels moisture and helps keep sensitive skin dry."

Calcium undecylenate is discussed for its antibacterial claims in this document and for its antifungal claims in the document on OTC antifungal diaper rash drug products, published elsewhere in this issue of the **Federal Register**. Talc and skin protectant claims are discussed in the document on OTC skin protectant diaper rash drug products, published elsewhere in this issue of the **Federal Register**. Boric acid is discussed in comment 7 above.

Undecylenic acid and its salts (for a total undecylenate concentration of 10 to 25 percent) were recommended as Category I ingredients for use in the treatment of athlete's foot, jock itch, and ringworm by the Antimicrobial (II) Panel (March 23, 1982; 47 FR 12480). That Panel recommended the following warning for all OTC antifungal ingredients: "Do not use on children under 2 years of age except under the advice and supervision of a doctor." That Panel was also concerned about the use of any antifungal agent indefinitely in the groin, because the groin is a sensitive area, and recommended labeling to limit products used for jock itch to 2 weeks only (47 FR 12490).

The Panel noted that undecylenic acid, an unsaturated fatty acid, is a normal constituent of human sweat (47 FR 12509). Fatty acids were first chosen 50 years ago for evaluation as topical therapeutic agents because they are found in sweat and therefore represent a more physiological method of treatment than the usual toxic antiseptic chemicals which may be more irritating (Ref. 6).

Based on the above Panel review and information, it appears that there may be no systemic toxicity hazard from topical absorption of calcium undecylenate. Nevertheless, the agency concludes that the submitted data are not sufficient to establish safety for topical OTC use for diaper rash in infants. Although the clinical studies in the submissions (Refs. 1 and 2) that are discussed below for efficacy suggest that a concentration of up to 15 percent calcium undecylenate would not be irritating for use on infants with diaper rash, they did not include specific tests for irritation or sensitizing potential such as patch-testing. The agency concludes that before calcium undecylenate can be considered safe for

OTC use in diaper rash drug products, studies are needed to determine the skin irritation and sensitization potential in infants when this ingredient is applied chronically under occlusion as occurs in the diaper area.

As part of the agency's Drug Efficacy Study Implementation (DESI) program, the National Academy of Sciences-National Research Council (NAS–NRC) Panel on Drugs Used in Dermatology II evaluated the ointment containing 15 percent calcium undecylenate and the powder containing 15 percent calcium decylenate and 3 percent boric acid and concluded that the ointment was effective for the treatment of diaper rash, chafing, minor skin irritations, and prickly heat, and that the powder product was effective for the prevention and treatment of diaper rash, prickly heat, chafing, and minor skin irritations and for the prevention and treatment of irritation due to incontinence" (Ref. 7). Reports by Litter (Ref. 8) and Sezar and Keitel (Ref. 9) were cited as supporting documentation. Subsequently, in the **Federal Register** of September 17, 1971 (36 FR 18599 to 18600), the agency stated its position on the NAS–NRC report and classified the above label claims as "possibly effective." Agency action regarding these products under the DESI program was subsequently deferred to the OTC drug review (January 11, 1974; 39 FR 1580).

In response to an agency request, additional studies, both published and unpublished, were submitted (Ref. 3) specifically to demonstrate the antibacterial and antifungal activity of undecylenic acid and its salts for use on diaper rash. In vitro studies using 5, 10, and 15 percent calcium undecylenate demonstrated significant zones of inhibition of *S. aureus, Staphylococcus epidermidis, E. Coli,* and *Pseudomonas aeruginosa* (*P. aeruginosa*).

The submissions to the advisory review panels (Refs. 1 and 2) included summaries of clinical studies and related case histories describing the use of a powder product containing 5 percent boric acid and 15 percent calcium undecylenate on infants with diaper dermatitis. The submissions reported that successful therapeutic results were obtained in most cases. In the in vivo study by Litter (Ref. 8), 200 infants and children aged 1 month to 5 years with various skin lesions, which included diaper rash, were studied. One hundred of the infants were treated with a 15-percent calcium undecylenate/3 percent boric acid product in a neutralized talc base and the remaining infants were treated with cornstarch or a bland baby powder and served as the control group. Cultures from the 100-treated infants were taken and examined. Bacteria were cultured in 38 of the treated cases, although the bacteria were not identified. Of the 38 cases in which bacteria were cultured, treatment with the powder product resulted in improvement rated as excellent in 16 cases, moderate in 18 cases, and slight in 4 cases. Litter reported that the skin irritations in the control group lasted 2 to 3 times longer than in the treatment group; however, the base in the control product was not the same as that in the treatment product.

One large-scale clinical investigation (Ref. 10), conducted in a hospital for a three-month period, involved 282 infants admitted with clear skin who were given daily prophylactic diaper care and after bath care which included a powder product. A powder containing 5 percent boric acid and 15 percent calcium undecylenate was applied to 168 infants; 21 of these infants (12.5 percent) developed rashes during the course of the study. A powder containing only 5 percent boric acid was applied to a control group of 114 infants; 24 of these infants (21 percent) developed rashes. The manufacturer contended that these results showed a reduction of 68 percent in the incidence of diaper rash in the calcium undecylenate group as compared to the control group.

Another study, by Robinson (Ref. 11), included 143 infants, ranging in age from 2 weeks to 23 months, selected at random from patients attending a well-baby clinic. Seventy-three of these infants had no evidence of a skin eruption. Contact dermatitis of the diaper area was present in 26 infants, and intertriginous eruptions, noncontact in origin, were present in 44 infants. The product used was a powder containing 15 percent calcium undecylenate, 3 percent borax acid, and 81.75 percent talcum. However, no placebo product was used. Mothers were instructed to apply the powder lightly, without rubbing, to the diaper area each time the diapers were changed. The infants were bathed with a mild soap and thoroughly rinsed. Diapers were washed in mild soap flakes and rinsed 3 times with warm clear water. Baby oils, creams, and lotions were not used. The infants were cleansed with clear water or mineral oil following bowel movements. Use of plastic or rubber pants was discouraged. Of the 70 infants with diaper rash or intertriginous eruptions, 60 were definitely improved, 8 remained unchanged, and 2 developed evidence of local irritation, which subsided when the powder was discontinued. Sixty-nine of the infants with no skin eruptions did not develop any eruptions; 4 of these infants had irritation. The institution of the cleanliness regimen was considered to be a major factor in producing the high percentage of satisfactory results. Robinson concluded that the powder is of value in mild diaper rash in infants. Also, because of its low sensitizing potential, the author stated that it is superior to baby powders containing various antiseptics which have irritating properties.

None of the submitted studies concerned the use of a product which used calcium undecylenate as the sole antimicrobial active ingredient. In addition, the studies described a powder product containing 15 percent calcium undecylenate. The currently marketed product contains only 10 percent calcium undecylenate, and there are no clinical effectiveness studies to support this concentration. Therefore, none of the data submitted provides sufficient evidence to establish the effectiveness of 10 percent calcium undecylenate for diaper rash use.

The agency is also concerned about the effect of calcium undecylenate on the skin flora under the occlusive conditions found in the diaper area when this ingredient is used chronically on infants and children. The agency believes that further in vivo bacteriological studies are needed, specifically in infants, to demonstrate the effect of the antibacterial activity of calcium undecylenate on the skin flora and whether this correlates with clinical improvements in diaper rash, and further whether long-term use of calcium undecylenate results in potentially harmful changes in the normal flora of the skin in the diaper area.

Accordingly, the agency is classifying calcium undecylenate for use in diaper rash drug products for antibacterial claims in Category III for both safety and effectiveness.

References

(1) OTC Volumes 160236.

(2) OTC Volumes 070021.

(3) Comment No. RPT005, Docket No. 75N-0183, Dockets Management Branch.

(4) Letter from J.L. Miller, Pennwalt Corporation, Pharmaceutical Division, to L. Geismar, FDA, dated December 28, 1987, in OTC Volume 02DTFM, Docket No. 75N-183D, Dockets Management Branch.

(5) OTC Volume 070029.

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(7) Rostenberg, A., "Caldesene," National Academy of Sciences—National Research

Council, Drug Efficacy Study, NDA 8967, Log 602.

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(10) Vignec, A.J., "Report on Prophylactic and Therapeutic Use of Desenex Baby Powder for a Three-Month Period Ending November 1," pp. 83–116, in OTC Volume 160236.

(11) Robinson, H.M., Jr., "A Study of a Protective Powder," *Southern Medical Journal*, 52:1421–1422, 1959.

F. Comment on Chloroxylenol

9. A submission to the Miscellaneous External Panel (Ref. 1) requested Category I status for a product containing 0.5 percent chloroxylenol (parachlorometaxylenol) in combination with 0.2 percent aluminum dihydroxy allantoinate and 45 percent microporous cellulose for the prevention of diaper rash. The submission included general safety data and in vitro antimicrobial effectiveness data on chloroxylenol and the combination product. Another submission (Ref. 2), which was made to the Antimicrobial I Panel, included data on a 5-percent chloroxylenol solution used at various dilutions as a diaper soak and as a solution applied directly to the skin to prevent and treat diaper rash.

The agency has reviewed the safety of chloroxylenol in the rulemakings for OTC topical antimicrobial drug products (43 FR 1210 at 1222 and 1238) and OTC antifungal drug products (54 FR 51136 at 51139). In the antifungal rulemaking, the agency proposed that chloroxylenol is safe for short-term use on small areas of the body. However, this finding is not considered adequate for a diaper rash drug product which should be shown safe for long-term use over large areas of the body.

The Antimicrobial I Panel, noting that only the most superficial toxicity data in animals was submitted for its review, placed chloroxylenol in Category III for all antiseptic uses (39 FR 33103 at 33134). The Panel stated its view that toxicity in rodent and non-rodent species, substantivity, blood levels, distribution and metabolism as well as any systemic absorption studies must be characterized before the ingredient could be considered for placement in Category I. The Panel was particularly concerned about the safety of using chloroxylenol in infants and recommended the warning: "not to be used on infants under six months of age." The Panel noted that chloroxylenol is metabolized by glucuronide and sulfate conjugation and there is a reported deficiency of metabolic conjugating mechanisms in infants. The Panel recommended that a toxicological evaluation of chloroxylenol should include studies to demonstrate safety in animals deficient in these detoxification mechanisms. The Panel stated that the effect of impaired liver function on elimination and toxicity would be important because the liver is considered a major organ for conjugation (39 FR 33134).

In the tentative final monograph for OTC topical antimicrobial drug products (43 FR 1210), the agency affirmed the conclusions of the Antimicrobial I Panel that chloroxylenol should not be used on infants until additional safety studies are conducted. The agency also proposed a warning not to use chloroxylenol-containing products on infants under 6 months of age unless such studies are conducted (43 FR 1238). As discussed in comment 3 above, the agency believes a diaper rash drug product should be safe for use on infants of all ages. Therefore, the agency does not consider a warning not to use a diaper rash drug product containing chloroxylenol on infants under 6 months of age adequate to support safe OTC use. Appropriate studies need to be conducted to demonstrate that chloroxylenol in a diaper rash drug product can be considered safe for use on infants of all ages.

The Antimicrobial II Panel categorized chloroxylenol (0.5 to 3.75 percent) as safe (Category I) for short-term use (up to 13 weeks) in OTC antifungal drug products. The Panel was concerned about the effect of chronic administration of chloroxylenol on the liver, but did not consider that topical application of chloroxylenol to small areas of the skin over short periods of time would result in liver damage (47 FR 12534 to 12535). In the tentative final monograph for OTC antifungal drug products (54 FR 51136 at 51139), the agency affirmed the conclusions of the Antimicrobial II panel to limit the use of chloroxylenol to 13 weeks because possible liver effects may become significant with long-term (repeated/daily) exposure times. The agency has determined that additional data characterizing the level of absorption, metabolism, and excretion following topical administration are needed to assess the safety of the chronic topical use of chloroxylenol (Ref. 3).

Data were submitted to the rulemaking for OTC topical antifungal drug products (Refs. 4 through 7) in response to agency concerns about the sensitization and irritation potential of chloroxylenol (Ref. 8). The data, submitted for an OTC topical antifungal drug product containing 2 percent chloroxylenol, consist of primary skin and eye irritation in rabbits (Refs. 4 and 5), a repeated insult patch test to the groin of ten adults (Ref. 6), and a clinical study of the effectiveness of the product (Ref. 7). In the tentative final monograph for OTC antifungal drug products, after reviewing the submitted data, the agency concluded that 2 percent chloroxylenol does not appear to have a potential for sensitization or irritation (54 FR 51136 at 51139). While the agency considers the studies supportive of the lack of irritation or sensitization potential for the ingredient, they are not adequate to demonstrate the lack of such potential when the ingredient is applied chronically under occlusion as occurs in the diaper area.

Chloroxylenol is a chlorinated phenol and has been shown to have a low level toxicity compared with other chlorinated phenolic compounds (Ref. 9). Phenol (see comment 16 below) and other phenol derivatives, such as hexachlorophene (see comment 10 below) and resorcinol (see comment 17 below), have also caused severe systemic toxicity, including death, in infants when applied externally, even in relatively low dilutions. Accordingly, the agency believes particular caution is needed when considering the topical use of any phenolic compound on infants.

Green and Preece (Ref. 10) conducted a study in rats on the toxic effects of maximal body exposure of chloroxylenol. In this study, rats were shaved and immersed for 30 minutes with only the head protruding in baths containing various dilutions of a chloroxylenol containing antiseptic. When immersed, the rats struggled, became comatose, and, particularly for the higher concentrations, lost consciousness and died during or after immersion. There was severe reddening externally and internally in the affected animals with the skin irritation resembling scalding. With 10 adult rats, which were observed for 7 days, of 8 deaths, 5 occurred within 2 hours, 2 more within 24 hours, and 1 more within 48 hours after exposure to a 3.2 or 5.14 percent antiseptic formulation. With 10 infant rats, which were observed for 24 hours, all 9 deaths occurred within 1 hour after exposure to a 4.95 or 7.86 percent antiseptic formulation. The authors stated that there was no evidence that infant rats were more susceptible than adult rats. Because the antiseptic preparation also contained terpineol and isopropyl alcohol in the vehicle base, it could not be determined which ingredients caused the deaths.

Therefore, Preece (Ref. 11) conducted a similar follow-up study in adult rats using the vehicle base only (no chloroxylenol). The same effects of reddening of the skin with unconsciousness and death occurred. The skin irritation was similar but less severe than that which occurred with the complete formulation. The difference in the results was that the vehicle base caused deaths at concentrations of 12.5 and 20 percent, while the product containing the chloroxylenol caused deaths at 3.2 and 5.14 percent concentration. Therefore, it has been shown that the chloroxylenol contributed to the toxicity of the complete antiseptic formulation.

The agency does not find this study adequate to determine the toxicity of chloroxylenol because the chloroxylenol was not tested alone but in combination with other toxic ingredients. Nevertheless, the study does raise questions concerning the safety of chloroxylenol, particularly regarding possible skin irritation or systemic absorption, when used over large areas of the body.

The agency received one study that included data on the distribution and metabolism of chloroxylenol in rats with a deficient glucuronidation mechanism (Ref. 12). In an effort to determine the contribution of the systemic toxicity of chloroxylenol to the toxicity observed in the above immersion study (Ref. 10), Havler and Rance studied the distribution and metabolism of ^{14}C-chloroxylenol in Sprague-Dawley and UDP-glucuronyl transferase deficient Gunn-Wistar rats after the intravenous, intramuscular, subcutaneous, and oral administration of the labeled ingredient in solution and in a marketed antiseptic. The authors concluded that the study's failure to approach the brain levels of the free phenol found in the immersion studies made it impossible to estimate the contribution of the systemic toxicity of chloroxylenol in the immersion study. They further reported that there was no significant difference between the two strains of rats with respect to the plasma and brain levels of free chloroxylenol attained in the study and that this similarity was further confirmed by the excretion route and metabolic excretion products. They concluded that the metabolic profiles for both strains of rats had been shown to be similar even though the Gunn-Wistar rat is incapable of performing many conjugation reactions due to a deficiency in UDP-glucuronyl transferase activity and that both strains of rats rapidly metabolized the ingredient largely as the glucuronide conjugate.

The data presented by the study are not sufficient to support the authors' conclusions. The study contains no actual data; it contains only summary material that is incomplete. The number of animals studied, gender, and age of the animals are not specified in the study, and the assay method used in the study is insensitive. Moreover, use of the Gunn-Wistar rat model is questionable because both stains conjugated the ingredient to the glucuronide to virtually the same extent, which suggests that the study was compromised either by method or strain. The study also does not address the effect of topical absorption through normal or irritated skin because the study was not conducted using topical administration. Therefore, the study is not considered adequate to demonstrate the safety of using chloroxylenol on infants under 6 months of age. Additional data from studies involving the topical administration of the ingredient to a large surface area of animals deficient in metabolic conjugating mechanisms (such as immature rats or neonate monkeys) are needed to demonstrate the safety of chloroxylenol for use in diaper rash drug products. In these studies, the chloroxylenol and metabolite levels should be determined by state of-the-art analytical techniques, with the single-dose and steady-state pharmacokinetics and tissue distribution determined over at least a four-hour period.

The agency has determined that studies need to be done to determine the degree of absorption from broken skin and from intact skin (as evidenced by blood levels) and the relationship between these blood levels and the blood concentration that produces no adverse effect in animals. In addition, studies are needed to determine the skin irritation and sensitization potential in infants when the ingredient is applied chronically under occlusion as occurs in the diaper area.

In conclusion, the agency has not been presented with sufficient safety data to classify chloroxylenol in Category I for use in diaper rash drug products. Such products are used on a relatively large area of the infant's body, are used under occlusion, and may be used for prolonged periods of time. The following types of data are needed to show that chloroxylenol is safe under such conditions of use:

(1) Studies in animals deficient in metabolic conjugating mechanisms (such as immature rats or neonate monkeys) to assess the metabolism, distribution, and elimination of chloroxylenol in infants under 6 months of age,

(2) Absorption studies of chloroxylenol applied to small and large areas of broken skin and intact skin as evidenced by blood levels and the relationship between these blood levels and the levels that produce no adverse reactions in animals,

(3) Local effects on sensitizing and irritation potential, and

(4) Potential for hypersensitivity in infants as can occur with other phenolic compounds.

Regarding efficacy, Joseph (Ref. 13) evaluated a solution containing 5 percent chloroxylenol and 10 percent terpineol along with a soap prepared from castor oil and oleic acid by saponification with potassium hydroxide in a 20-percent solution of alcohol in water. Dilutions of this 5 percent chloroxylenol solution were found to be more active than similar dilutions of methylbenzethonium chloride for in vitro activity against urea-splitting bacteria such as *B. ammoniagenes, Proteus vulgaris (P. vulgaris),* and *P. mirabilis.* Joseph stated the the chloroxylenol solution has high antibacterial action against the above bacteria up to a dilution of 1:6,000 and was not inactivated by the presence of foreign protein. Joseph demonstrated that residual germicidal action remained in diapers laundered with a final rinse containing 2 tablespoonfuls of the above 5 percent chloroxylenol solution per gallon of water. Joseph also reported on the use of chloroxylenol solution in the relief and prevention of ammonia dermatitis. Twelve children (age 6 to 18 months) with diaper rash were treated by direct skin application of a dilute chloroxylenol solution (1:100) three times a day until improvement was noticed; then the solution was applied twice a day. All cases cleared after 5 days. After the rash cleared, direct skin application was stopped, and the chloroxylenol solution was used on laundered diapers as a final rinse to impregnate the diapers. After 3 weeks, all children showed a reduction in the incidence and severity of diaper rash and 9 of the cases had cleared. In three severe cases, there was improvement after 3 weeks of using chloroxylenol impregnated diapers but the rash did not clear. Joseph does not explain why the same children with severe diaper rash that cleared after 5 days of direct skin application did not show clearing of the rash after a subsequent 3 weeks of use of impregnated of diapers. This study suffers from an inadequate definition of diaper rash and no definition of

parameters for improvement. In addition, this study was a total formulation study. It does not show the contribution of the chloroxylenol to the product and no control formulation was used. The study also does not include microbiological culture to clarify whether the use of chloroxylenol results in potentially harmful changes in the normal flora of the skin in the diaper area. Therefore, the agency does not find these data adequate to demonstrate the effectiveness of chloroxylenol for diaper rash claims. Based upon the above discussion, the agency is classifying chloroxylenol for use in diaper rash drug products in Category III for both safety and effectiveness.

Regarding the combination product containing chloroxylenol, aluminum dihydroxy allantoinate, and microporous cellulose, the agency notes that the product no longer contains chloroxylenol or aluminum dihydroxy allantoinate (Ref. 14). At this time, any combination product containing chloroxylenol labeled with diaper rash claims is considered Category III.

References

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G. Comments on Hexachlorophene

10. Several submissions to the Antimicrobial I Panel (Ref. 1) and comments to the antimicrobial I rulemaking (Ref. 2) claimed hexachlorophene was safe and effective for use on infants for such claims as total body bathing to prevent staphylococcal infections and to treat or prevent diaper rash. Some of the submissions objected to the agency's proposed statement of policy (January 7, 1972; 37 FR 219) and final rule (September 27, 1972; 37 FR 20160) on hexachlorophene that limit all products containing more than 0.1 percent hexachlorophene to prescription use. The comments objected to the Antimicrobial I Panel's classification of hexachlorophene in Category II in its advance notice of proposed rulemaking for OTC topical antimicrobial drug products (September 13, 1974; 39 FR 33103). One comment to the tentative final monograph for OTC antimicrobial drug products objected to the agency's statement, at 43 FR 1213, that the Commissioner "sees little or no need to use antimicrobial soaps on infants." The comment cited previously submitted data which demonstrate that hexachlorophene-containing bar soaps, powders, lotions, and solutions reduce staphylococcal infections in the nursery and are helpful in the prevention and management of diaper rash. The comment stated that between 1949 and 1972 many hundreds of thousands of newborn infants routinely underwent antiseptic care (total body bathing) with hexachlorophene preparations. According to the comment, this use resulted in the reduction and control of staphylococcal cross-infection and sepsis in newborns. Several submissions stated that the need and benefits derived from hexachlorophene products have been clearly documented by the staphylococcal epidemics that followed the removal of hexachlorophene products from hospital nurseries in 1971 as a result of FDA action. One of the comments submitted additional data to support the safety of hexachlorophene in infants, including a retrospective study by Plueckhahn and Collins on 3 percent hexachlorophene in baby bathing (Ref. 3), an unpublished study by Plueckhahn of hexachlorophene blood levels in infants receiving routine antiseptic skin care (Ref. 4), and a comprehensive review article by Plueckhahn on the safety and effectiveness of hexachlorophene in infants (Ref. 5). While acknowledging that toxicity can result from use of 3 percent hexachlorophene in premature infants or infants with skin excoriations, or from the use of high (6 percent) concentrations of hexachlorophene, this comment nevertheless contended that the value of hexachlorophene far exceeded its drawbacks. The comment specifically quoted Plueckhahn's and Collins' conclusions (Ref. 3) that "there is no rationale for restricting the dermal use of 3 percent hexachlorophene emulsions in the care of normal infants."

The agency agrees that the submitted studies indicate that hexachlorophene 3 percent can be effective in preventing staphylococcal skin infections in infants. Hexachlorophene may also be effective in preventing or treating diaper rash (Refs. 6 through 10). Nevertheless, as discussed below, the agency is not classifying hexachlorophene in Category I for OTC use in infants because its toxicity prevents safe use by the layman.

The deaths of 36 infants were reported in France in 1972 from poisoning by a topical baby powder inadvertently contaminated with up to 6 percent hexachlorophene (Ref. 11). Goutieres and Aicardi (Ref. 12) reported on 18 children between 3 months and 3 years of age with normal skin who were accidently intoxicated by this hexachlorophene-contaminated powder. Four cases with spinal cord involvement died of cardiorespiratory arrest and two others remained paraplegic. The powder had been applied to the napkin area several times a day and allowed to remain between changes. Seventeen of the children developed severe erythema in the napkin area resembling second-degree burns. Erythema preceded the neurological signs by 3 to 15 days in 6 cases, followed the neurological signs in 4 cases, and occurred simultaneously or at unknown times in the remaining cases. The authors felt that the higher concentration hexachlorophene, the prolonged contact with the skin, and the cutaneous erosion induced by hexachlorophene may have all resulted in increased absorption of hexachlorophene.

Shuman, Leech, and Alvord (Refs. 13 and 14) conducted a retrospective pathological study in human infants who died of other causes and showed a correlation of brain lesions with hexachlorophene-bathing. Bruch (Ref. 15) notes that topically applied hexachlorophene was proven to result in levels of hexachlorophene in the body high enough to be able to produce neurologic disorder and morphologic changes.

Several investigators have noted that the risk of hexachlorophene toxicity increases in the presence of dermal rashes, abrasions, burns, or wounds (Refs. 11, 12, 16, and 17). Maibach and Hacker (Ref. 18) have also suggested that the regular use of antibacterial agents such as hexachlorophene on the easily penetrated skin of the scrotum may be a significant cause of inflammation leading to secondary infection.

With whole body bathing of infants to prevent staphyloccal skin infections, most recommendations would limit such use to only specific situations in hospital nurseries. For example, as noted above Shuman, Leech, and Alvord (Refs. 13 and 14) found that repeated whole body bathing (by applying an undiluted preparation containing 3 percent hexachlorophene to the whole body except the face) in premature infants correlated with lesions in the brainstem reticular formation. The authors concluded that, based on their findings, hexachlorophene should not be used at all in the small premature infant and the amount used in near-term or full-term infants should be markedly decreased and rinsed off thoroughly.

Imperato (Ref. 19) recommended prophylactic daily bathing of healthy newborn infants using 3 percent hexachlorophene as a control measure during a staphylococcal epidemic in a hospital nursery. Imperato also recommended that hexachlorophene bathing should be discontinued upon discharge from the nursery, and stated that no hexachlorophene-containing preparation should routinely be provided for bathing at home.

The Committee on Fetus and Newborn of the American Academy of Pediatrics agreed that during outbreaks of epidemics of *S. aureus* infection in a hospital nursery, one possible measure undertaken could be brief institution of a program of total body bathing with a solution of not more than 3 percent hexachlorophene (Refs. 20 and 21). Under this program, the application would be limited to full-term infants, thoroughly washed off after the application, and applied no more than two times to each infant.

In the tentative final monograph for OTC topical antimicrobial drug products (42 FR 1210 at 1220), the agency, in response to a comment objecting to the classification of hexachlorophene as a prescription drug, concluded that there was no convincing basis for changing the ingredient's classification as set forth in the Federal Register of September 27, 1972 (37 FR 20160).

The agency does not consider the additional data submitted by the comment as sufficient to support the safe use of hexachlorophene on infants. The agency finds a lack of sufficient data to support the conclusion reached by Plueckhahn and Collins that the benefits of the use of hexachlorophene in normal newborn infants far outweigh any possible risks from central nervous system vacuolation (Ref. 3). The study which serves as the basis for their conclusion lacks essential details of hexachlorophene usage, such as the amount of hexachlorophene used, the length of exposure, rinsing methods, if any, and frequency of application. Plueckhahn and Collins concluded that infants having a low birth weight (less than 2,000 grams (g)) were susceptible to central nervous system vacuolation after hexachlorophene skin care; however, the agency finds that they made no comparison of skin conditions or physical differences between infants weighing less than 2,000 g and those weighing more than 2,000 g. Although this study suggests that a low birth weight may account for the development of vacuolation, the data are insufficient to support this theory.

Plueckhahn and Collins also state in their study (Ref. 3) that it is possible the central nervous system vacuolation "is not directly due to high blood and tissue hexachlorophene concentrations and is not a measure of neurotoxicity." They contend that the vacuolation may be a transient edema without overt symptomatology. However, this conclusion was not substantiated by the data, and extensive behavioral tests on animals exhibiting such histological changes would be essential to substantiate the authors' conclusion. The agency is aware of one such study conducted in rats where orally administered hexachlorophene was shown to have an adverse effect on behavior and other central nervous system functions even after the drug was discontinued and the animals appeared normal (Ref. 22).

The unpublished study by Plueckhahn (Ref. 4) involved 152 infants weighing more than 2,000 g who received routine antiseptic skin care with 3 percent hexachlorophene. The blood hexachlorophene concentration obtained by "heel pricks" reached a plateau of about 0.3 parts per million (ppm) after three or more washings and did not increase significantly with additional washings. However, this study failed to report the skin condition, weight, or blood levels of the individual infants tested.

The review article contained an unpublished study by Plueckhahn (Ref. 5) that discussed two groups of infants who received routine antiseptic skin care with either 3 or 0.75 percent hexachlorophene. The blood analysis showed absorption of hexachlorophene, with lower blood levels after use of 0.75 percent hexachlorophene than with 3 percent hexachlorophene. Plueckhahn concluded that hexachlorophene blood levels reach a maximum during the first week of skin care. The agency believes that this statement should be qualified to point out that, with the limitations of the study, the observation of maximum blood levels of hexachlorophene are reached within 1 week. Only 22 of the 722 blood specimens were taken after 8 days. Deficiencies in the study are that skin area, skin condition, weight of infant, and rinsing techniques were not described. Also, the blood level data appear to contradict the suggestion made in the study described above (Ref. 3) that infants weighing more than 2,000 g do not absorb enough hexachlorophene to cause central nervous system vacuolation. The data show increasing blood levels of hexachlorophene through day 7 or 8 even though applications were made only on alternate days (Ref. 5). Other data reviewed by the agency suggest rapid metabolism and elimination (Ref. 23), but these data from alternate day applications make the metabolism data a weaker case.

Another study in the review article listed blood hexachlorophene concentrations for 33 infants receiving routine skin care with 0.5 percent hexachlorophene talcum powder for 9 to 14 days (Ref. 5). The ages of the babies were not listed and the frequency of the diaper area powdering cannot be determined from the data presented. Furthermore, an increasing blood concentration with time can be observed in many of the infants studied, but the author did not reach any conclusions from this particular study.

One conclusion by Plueckhahn is that "immediate or long term adverse clinical effects or neurological manifestations have not been seen in low birth weight infants with blood hexachlorophene concentrations ranging from 0.690 ppm to 1.59 ppm during routine antiseptic skin care" (Ref. 5). In the earlier study

(Ref. 3), Plueckhahn and Collins briefly discussed 12 infants from 2 separate studies who received a total body bathing with hexachlorophene at least four times and then were followed-up clinically for 2 to 12 years. The infants were reported to have developed normally, but no details of the follow-up were presented.

The agency does not find the limited long-term data adequate proof that there are no long-term adverse effects from hexachlorophene usage. The agency also questions the author's statement that "spongy vacuolation during routine antiseptic skin care with 3.0 percent hexachlorophene emulsions does not occur in normal newborn infants weighing more than 2,000 g at birth" (Ref. 3). This statement was based solely on the results of infant autopsies and cannot be applied to normal newborns.

Under existing agency regulations in 21 CFR 250.250, hexachlorophene is contraindicated for use on burned or denuded skin or on mucous membranes and for routine prophylactic total body bathing. Based on this regulation and the discussion above, the agency also concludes that hexachlorophene is contraindicated to either prevent or treat diaper rash. The agency further restates that total body bathing of infants to prevent staphylococcal skin infections for specific situations in hospital nurseries should be limited to use only under medical supervision with appropriate labeling for safe and effective use by practitioners as described under § 250.250.

The agency concludes that hexachlorophene is Category II for OTC drug products with diaper rash claims or other claims concerning prevention of staphylococcal skin infections in infants because of safety risks.

References

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(23) SUP013, Docket No. 75N–0183, Dockets Management Branch.

H. Comments on Methylbenzethonium Chloride

11. Several submissions to the Antimicrobial I Panel (Ref. 1), the Antimicrobial II Panel (Ref. 2), and the Miscellaneous External Panel (Ref. 3) were for products containing methylbenzethonium chloride with diaper rash claims. The products included an ointment containing 0.1 percent methylbenzethonium chloride, zinc oxide, calamine, and eucalyptol; a cream containing 0.1 percent methylbenzethonium chloride, 20 percent zinc oxide, 5 percent cod liver oil with vitamins A and D, and 5 percent calcium caseinate powder; an ointment containing 0.1 percent methylbenzethonium chloride, 17.5 percent white petrolatum, and 12 percent glycerin; a lotion containing 0.068 percent methylbenzethonium chloride in a water and oil emulsion with an oxycholesterin absorption base and magnesium citrate; a lotion containing methylbenzethonium chloride, methylparaben, propylparaben, and chlorobutanol; and a powder containing 0.059 percent methylbenzethonium chloride in a corn starch base.

A submission from one company (Ref. 4) included labeling bearing general antiseptic claims such as "antiseptic ointment—aids in the prevention and treatment of irritated skin in such conditions as diaper rash * * *."

A second company with submissions for several products (Ref. 5) focused on ammonia dermatitis in diaper rash, and stated that methylbenzethonium chloride, when released from ointment, cream, and powder bases, or from impregnated diapers, acts presumably by killing microorganisms in urine and feces that produce ammonia and other (as yet, unspecified) irritating agents. This company contended that the consistent finding in the controlled clinical studies in its submissions is that methylbenzethonium chloride is an effective agent for the treatment of ammonia dermatitis and that it can be used prophylactically as a means of reducing the incidence of ammonia dermatitis.

Methylbenzethonium chloride has been reviewed for safety for topical use in two other OTC drug rulemakings. In the advance notice of proposed rulemaking for OTC topical antimicrobial drug products (September 13, 1974; 39 FR 33103), the Antimicrobial I Panel concluded that this ingredient and two other quaternary ammonium compounds at a concentration not greater than 1:750 (0.13 percent) could be

regarded as safe as a skin wound cleanser provided that the product is not used repeatedly, covered with occlusive bandaging, or used in deep or extensive wounds (39 FR 33116). However, the Panel concluded that further toxicity data characterized by the absorption and systemic toxicity in a rodent and nonrodent species should be generated prior to the placement of these quaternary ammonium compounds into Category I for use other than as a skin wound cleanser (39 FR 33132). In the tentative final monograph for OTC topical antimicrobial drug products (January 6, 1978; 43 FR 1210), the agency did not include recommendations for further animal studies and stated that the systemic toxicity of quaternary ammonium compounds in animals is low and is indicative of and reflects the surfactant nature of the molecule (43 FR 1236). The agency stated that even though specific absorption and systemic levels in humans have not been reported for the three quaternary ammonium compounds reviewed, considering the concentrations applied, and extrapolating from animal studies, toxic effects at use levels would be unlikely (43 FR 1237). However, both the Panel (39 FR 33132) and the agency (43 FR 1237) noted that there are many reports on the irritating nature of the quaternary ammonium compounds on the skin, mucous membranes, and the eye and that the degree of irritation increases when quaternary ammonium compounds are used under occlusion.

OTC topical use of methylbenzethonium chloride for controlling cradle cap was reviewed by the Miscellaneous External Panel in the advance notice of proposed rulemaking for OTC drug products for the control of dandruff, seborrheic dermatitis, and psoriasis (December 3, 1982; 47 FR 54646 at 54677). The Panel evaluated a submission (Ref. 6) for a product containing methylbenzethonium chloride 0.07 percent in an emulsified petrolatum base with label directions to apply 3 times daily for 3 days for treatment of cradle cap and to apply 3 times weekly to prevent recurrence. The Panel concluded that this product was safe for controlling cradle cap (47 FR 54677).

NDA's were approved on the basis of safety for two OTC drug products containing methylbenzethonium chloride for use on infants for diaper rash: one in 1947 for a diaper impregnator rinse (1:25,000 dilution) (Ref. 7), and the other in 1948 for a topical diaper rash ointment at a 0.1 percent concentration (Ref. 8). While there have been reports of skin irritation or necrosis resulting from topical treatment, especially under occlusion, with other quaternary ammonium compounds (Refs. 9 through 12), there is little evidence that this problem has occurred with methylbenzethonium chloride in the 40 years that it has been marketed for use for diaper rash.

The data in the submissions (Refs. 1, 2, and 3) to the OTC panels included reports of 17 controlled and uncontrolled trials involving over 7,000 subjects in which the use of various dosage forms (ointments, creams, lotions, powders, and solutions for topical use; and final rinses for diapers) of methylbenzethonium chloride were tested on over 4,000 infants and children to prevent or treat diaper rash (Refs. 13 through 26). In all these studies, there were no reports of adverse reactions attributable to methylbenzethonium chloride.

Several of these studies (Refs. 15, 20, and 24) were for a prolonged duration. For example, both Lipschutz and Agerty (Ref. 15) and Meadows (Ref. 20) studied the use of a prophylactic regimen for diaper rash that included daily use of hexachlorophene skin cleanser and methylbenzethonium chloride in a lotion, ointment, cream, or diaper rinse. Lipschutz and Agerty (Ref. 15) evaluated the prophylactic regimen on 200 children ranging from 2 months to 2½ years of age. Each child remained in the study for 6 months. The authors did not report any medical problems attributable to failure of the regimen and did not report any primary or secondary skin sensitivity. Meadows (Ref. 20) evaluated the same prophylactic regimen on 100 infants, beginning at birth and followed at regular intervals for 3 to 24 months (average 10.7 months). The author did not report any cases of intolerance to the skin care products and recommended that this home prophylactic antiseptic skin care should continue until the child is toilet trained.

Wahlberg (Ref. 11) reviewed the literature in 1962 and reported only 7 clinical cases of hypersensitivity to quaternary ammonium compounds. None of these cases involved methylbenzethonium chloride. In addition, 5 studies (Refs. 13, 16, 17, 19, and 22) included patch tests on a total of 450 infants and indicated that methylbenzethonium chloride was not a significant sensitizer. Lipschutz and Fischer (Ref. 16) used patches treated with methylbenzethonium chloride (1:1,800) in a corn-starch-base dusting powder and skin-tested 50 infants and children ranging in ages from 3 weeks to 5 years. The patches were left in contact with the skin on an unspecified place for 48 hours. One child developed an erythema that cleared in 48 hours. When the patches were reapplied 10 days later on the same children, no reactions were noted. These authors also reported that another investigator had found the methylbenzethonium chloride powder to be hypoallergenic. Chiara (Ref. 13) patch-tested 50 newborn infants with a lotion containing 0.068 percent methylbenzethonium chloride by applying gauze pads saturated with the lotion to the area between the scapulae and examining the areas after 48 hours. The patches were reapplied in 2 weeks and evaluated again after 48 hours. No evidence of irritation or sensitivity was noted in any of the infants. Grossman (Ref. 17) patch-tested 100 newborn infants with an ointment containing 0.1 percent methylbenzethonium chloride in a cod liver oil base. The patches were left on an unspecified area for 72 hours, removed for 1 week, and reapplied for 72 hours. No evidence of perianal sensitivity was noted.

Niedelman and Bleier (Ref. 19) patch-tested 50 infants and children with an ointment containing 0.1 percent methylbenzethonium chloride. The patch-test was applied in the usual manner on the back or on the arm with a half-inch square gauze covered with wax paper and held in place by adhesive tape. In 10 subjects the patch was removed after 24 hours, in 20 subjects after 48 hours, and in the remaining 10 subjects after 72 hours. There were no reactions to the ointment. Benson et al. (Ref. 22) patch-tested 180 children and infants and 20 newborn infants with a solution of 1:5,000 methylbenzethonium chloride on 1 inch square gauze patches that remained wet and in contact with an unspecified area of skin for 24 hours. In 100 of the infants and children, the patch test was repeated in 10 days. No irritating effects were noted. Maibach (Ref. 27) reported that minimal irritation was observed when 0.2 mL of a 0.5 percent methylbenzethonium chloride solution impregnated on a 2-centimeter square patch of nonwoven fabric was applied to the backs of adult volunteers and remained under occlusion for 21 days. Each patch was renewed every 24 hours after evaluation.

Most of the topical preparations studied (as described above) were at concentrations of 0.1 percent or less, although there were some reports of more concentrated preparations being used. For example, Vignec (Ref. 25) used an antiseptic liquid containing 0.5 percent methylbenzethonium chloride and other ingredients for 7 to 14 days on 138 infants suffering from diaper irritation, minor skin conditions, and

excoriation. He concluded that the drug was safe because at no time did it produce irritation or allergic reactions. Although this report suggested that concentrations up to 0.5 percent would not be irritating for use on infants for diaper rash, it only involved short-term use.

Although the Miscellaneous External Panel recommended that methylbenzethonium chloride is safe for use in treating cradle cap, other panels have raised concern about repeated use and use under an occlusive dressing. When used for treating and/or preventing diaper rash, the product is likely to be used for a long period of time, possibly over a large area and on more sensitive skin, and will be used under occlusion, i.e., diapers. However, with the exception of irritation tests conducted by Niedelman and Bleier (Ref. 19), which were done under occlusion, the authors of the other studies (Refs. 13, 16, 17, and 22) do not state whether or not occlusion was used in their tests to maintain the product in close contact with the skin. Also, the authors do not specify whether any of the patch-tests were applied to the infants' diaper area, which is more sensitive than other areas of the body. Therefore, the agency is not able to reach any conclusions about the sensitizing potential of the ingredient under the occlusive conditions found in the diaper area when this ingredient is used chronically on infants and children.

The agency has determined that additional data are needed to demonstrate the safety of methylbenzethonium chloride or other quaternary ammonium compounds for use in diaper rash drug products for chronic use on infants and children. Studies need to be done to determine the degree of absorption from broken skin (as evidenced by blood levels) and the relationship between these blood levels and the blood concentration that produces no adverse effect in animals. In addition, studies are needed to determine the skin irritation and sensitization potential in infants when the ingredient is applied chronically under occlusion as occurs in the diaper area.

As part of the agency's Drug Efficacy Study Implementation (DESI) program, the National Academy of Sciences-National Research Council (NAS–NRC) Panel on Drugs Used in Dermatology II evaluated the ointment product that contained 0.1 percent methylbenzethonium chloride. The NAS–NRC Panel also evaluated the diaper rinse product that contained 12.7 percent methylbenzethonium chloride (1 tablet diluted in 2 quarts of water, providing an approximately 1:25,000 solution for six diapers). The label claims for these products include: "quickly relieves diaper rash," "antibacterial," "prevent diaper rash," and "eliminates the cause of diaper rash (ammonia dermatitis)," (Refs. 28 and 29). The NAS–NRC Panel categorized both products as "effective but * * *" and explained that the products' efficacy was adequately documented, but the labeling implied that ammonia is the only cause of diaper rash, which is not the case. That Panel also stated that with appropriate rephrasing of the labeling, it could consider these products effective. Subsequently, in the **Federal Register** of July 3, 1971 (36 FR 12705), the agency stated its position on the NAS–NRC reports and classified these products as "possibly effective" in preventing diaper rash and eliminating the cause of diaper rash (ammonia dermatitis). The agency also stated that these products lacked substantial evidence of effectiveness when labeled for use as antiseptics, disinfectants, or general antimicrobial agents.

With respect to the claim for methylbenzethonium chloride use against diaper rash caused by ammonia-producing microorganisms, the agency concluded that the manufacturer needed to show efficacy against all the organisms that can produce ammonia. The agency also determined a need to demonstrate efficacy under use conditions, in vitro and in vivo, in the presence of appropriate inactivators, e.g., soap, anionic detergents, fecal material, urine, cotton, hard water. The agency was concerned about reports that quaternary ammonium compounds are readily inactivated by many substances that may be encountered during use in the diaper area, e.g., gauze, cotton, fecal material, blood, soap, dirt (Refs. 30 through 33). However, Walter (Ref. 34) questioned whether some of the reports of inactivation of quaternary ammonium compounds are accurate. He felt that these reports were based on inadequate dilutions and improper use of quaternary ammonium compound disinfectants, especially in hospitals.

The antiseptic action of methylbenzethonium chloride, a quaternary ammonium compound, can be altered by anionic detergents, including soap (Ref. 30). Accordingly, data were needed to show that antibacterial activity still occurred when topical products were applied to detergent- or soap-washed skin or when diapers that had been laundered with detergent or soap were treated with a diaper rinse containing methylbenzethonium chloride.

Subsequently, the company submitted additional information (Ref. 35) to the DESI rulemaking to show evidence of (1) activity of methylbenzethonium chloride against urea-splitting organisms other than *B. ammoniogenes* and *P. mirabilis*, specifically pseudomonas, micrococci, and diphtheroids, (2) residual antibacterial activity in diapers rinsed in methylbenzethonium diaper rinse after detergent or soap laundering, and (3) evidence of activity of methylbenzethonium chloride on the skin of infants washed with detergents or soaps. Agency action regarding these products under the DESI program was subsequently deferred to the OTC drug review (January 11, 1974; 39 FR 1580).

Regarding methylbenzethonium chloride activity against urea-splitting organisms other than *B. ammoniogenes* and *P. mirabilis*, the company contended that evidence of microbiologic activity of methylbenzethonium chloride against pseudomonas and various micrococci is amply supplied in articles by Nagamatsu, Johnson, and Silverstein (Ref. 36), and by Lawrence (Ref. 37). The Nagamatsu, Johnson, and Silverstein study was also cited by the NAS–NRC Panel to document its "effective but * * *" classification. This uncontrolled study involved the prophylaxis and treatment of 23 incontinent patients aged 39 to 75 years with skin excoriation, using a 1:5,000 solution of methylbenzethonium chloride to impregnate dressings, diapers, or towels. A water-miscible ointment containing 0.1 percent methylbenzethonium chloride was used as an adjunct where ulceration occurred. The authors chose this treatment method because they had found that a urinary culture of these patients always revealed the presence of ammonia-splitting organisms within the urine itself. They related this to Cooke's work on ammonia-caused diaper rash due to *B. ammoniogenes* and other studies on use of methylbenzethonium chloride impregnated diapers in children with diaper rash. The authors felt that if methylbenzethonium is equally effective against all the ammonia-producing organisms, then treatment with dressings impregnated with the ingredient would be equally effective treatment for their patients with urinary excoriation. The authors found methylbenzethonium chloride effective in vitro (using broth cultures) against all the urea-splitting organisms isolated from their patients. The authors

provided a table listing the bacteriostatic and bactericidal dilutions of methylbenzethonium chloride against some of the more common urea-splitting isolates, including *P. vulgaris, Streptococcus faecalis, Pseudomonas Pyocyanea, Alcaligenes faecalis, Aerobacter aerogenes,* and *S. viridans.* Lawrence (Ref. 37) found methylbenzethonium chloride to be more effective than neomycin in minimum inhibition concentration in vitro tests against all the gram-positive and gram-negative organisms tested, which included *B. ammoniagenes, S. aureus, Salmonella typhosa (S. typhosa), P. mirabilis, P. aeruginosa, Bacillus cereus (B. cereus), Bacillus subtilis (B. subtilis), E. coli, P. vulgaris, Salmonella cholerae-suis (S. cholerae-suis), Salmonella pullorum (S. pullorum),* and *Shigella dysenteriae (S. dysenteriae).* Although the company was unable to find any data on diphtheroids, the agency notes that Leyden (Ref. 38) has subsequently stated that *B. ammoniogenes* is a diphtheroid, for which in vitro data are available. Therefore, the agency agrees that these studies (Refs. 36 and 37) demonstrate that methylbenzethonium chloride has in vitro bacteriostatic activity against many ammonia-producing bacteria.

The agency does not, however, consider these data sufficient to establish effectiveness. In the discussion on Cooke's ammonia theory of diaper rash (see comment 2 above), it was noted that this theory has been questioned by more recent studies. Thus, any claims concerning the ammonia theory must be supported by clinical studies on infants that include bacteriological studies to correlate a reduction in ammonia-producing bacteria with a clinical improvement in the diaper rash (see comment 2 above). Therefore, in vitro tests are not sufficient to prove effectiveness for ammonia-caused diaper rash.

For a discussion of residual antibacterial activity in diapers rinsed in methylbenzethonium chloride after detergent or soap laundering, see comment 12 below.

As to activity of methylbenzethonium chloride on the skin of infants washed with detergents or soaps, the company stated that no studies were specifically directed to evaluating the effect of residual soap or detergent on babies' skin on the activity of its products. However, the company specifically cited the studies by Lipschutz and Fischer (Ref. 16) and Benson et al. (Ref. 23) as supporting successful prophylaxis or treatment of diaper rash presumably in the presence of residual soap or detergent on the skin.

The agency has evaluated the studies submitted by the company that were cited by the NAS-NRC Panel as well as other data submitted to the OTC drug review in which methylbenzethonium chloride was used to treat or prevent diaper rash. The following comments are limited to those drug products intended for direct application to the skin of infants. Studies on the use of methylbenzethonium chloride for diaper-rash-like skin conditions in incontinent adults are discussed in comment 13 below. Diaper rinses intended for use to treat diapers are discussed in comment 12 below.

The agency finds that the studies pertaining to the treatment or prevention of what is loosely referred to as diaper dermatitis suffer from the major defect of lack of definition. Diaper dermatitis is not a single entity, and none of the authors has given specific parameters for the diagnosis of the condition. In the studies on ammonia dermatitis, no attempts were made to assay levels of ammonia or ammonia-forming bacteria on the skin or diaper either before or after therapy.

Most of the studies were conducted in the late 1940's to early 1960's when the concept of a double-blind, controlled protocol was not as widely recognized as it is today. In many of these studies, instead of using a control of the vehicle without the active ingredient, some other preparation was used as the control, such as mineral oil, petrolatum, a product containing another antimicrobial ingredient, or soap and water. In addition, several of the other ingredients contained in the methylbenzethonium chloride-containing preparations are being reviewed as active ingredients in the skin protectant segment of the diaper rash rulemaking, with some being classified as Category I. Some examples are cod liver oil, zinc oxide, petrolatum, calamine, and corn starch. Because these skin protectant ingredients contribute a substantial benefit for treating or preventing diaper rash, appropriate vehicle controls must be used to support conclusions regarding methylbenzethonium chloride's contribution to the product's effectiveness. Furthermore, in several of the studies, more than one dosage form of methylbenzethonium chloride was used as part of a "skin care regimen." In some of the studies (Refs. 15 and 20), a hexachlorophene detergent skin cleanser was also used in addition to the various methylbenzethonium chloride products. Therefore, many of the studies are not considered adequate to establish the contribution of methylbenzethonium chloride.

Several studies (Refs. 13, 17, and 21) were conducted on newborn infants while still in the hospital. Two of the studies (Refs. 13 and 21) specifically stated and one study (Ref. 17) implied that regular soap and water baths were not given to the infants. This regimen is not typical of the conditions of home use of diaper rash products and would not answer agency concerns about the possibility of residual soap on the skin inactivating methylbenzethonium chloride.

Because of the various problems with the studies above, the agency believes the studies by Bleier and Niedelman (Ref. 14) and by Lipschutz and Fischer (Ref. 16) provide the most useful information. Bleier and Niedelman (Ref. 14) conducted a controlled study on 90 infants diagnosed as having ammonia dermatitis. Fifty-eight infants were treated with an ointment containing 0.1 percent methylbenzethonium chloride and 32 infants were treated with the ointment base alone as controls. The authors only stated that for the methylbenzethonium chloride group the treatment was 1 day to 3 weeks and did not specify any time period for the control group. The study was conducted in a hospital, and the medical and nursing staff were unaware of which ointment was being used. Although no criteria were given for the different grades of severity in the infants studied, the authors did group them as having mild rash or severe rash. Of the 58 infants treated with the active ingredient, 42 (72 percent) were classified as having mild diaper rash, while 16 (28 percent) were classified as having severe diaper rash. At the end of the treatment period, 53 percent were considered healed, 41 percent were improved, and 5 percent were not improved. The authors noted that improvement was most significant in the severe group, where 11 of 16 (69 percent) were healed and 5 (31 percent) were improved. Of the 32 infants in the control group, 12 (37 percent) had mild diaper rash and 20 (63 percent) had severe diaper rash. Although the authors did not state the time period of treatment in the control group, there was a 25 percent improvement (6 in the mild group and 2 in the severe group). The agency notes that there was a substantial disparity between the percent of infants who had severe dermatitis and received active treatment (16 of 58 or 28 percent) and those who received the vehicle control (20 of 32 or 63 percent). While the authors noted

that many antiseptics lose some of their activity in the presence of organic matter, they concluded that this study demonstrated that the ointment containing methylbenzethonium chloride was not inactivated on the skin.

Lipschutz and Fischer (Ref. 16) evaluated methylbenzethonium chloride in a corn starch dusting powder. In vitro bacteriological studies were performed and demonstrated that the growth of innoculated *B. ammoniagenes* was markedly inhibited in diapers that were dusted with the corn starch powder containing methylbenzethonium chloride. However, there was good growth of organisms in the control diapers that were dusted with either 5 percent borated talc or plain corn starch dusting powder. The authors then evaluated the use of the methylbenzethonium chloride corn starch dusting powder for the treatment of ammonia dermatitis and intertrigo in infants 3 months to 2 years of age. The criteria for diagnosis of ammonia dermatitis were location (areas of skin in contact with urine-soaked diapers or bed clothes), type of rash (mild, erythema; moderate, papular vesicular, pustular; severe, ulceration including meatus ulcer), and ammonia odor. The criteria for diagnosis of intertrigo were location (folds of skin, especially the groin), type of rash (erythema and exudation limited to the folds), and type of infant (usually obese infants improperly cleaned and bathed). All infants were treated for 10 days, with powder dusted on the infant after each diaper change and at bedtime (an average of seven times a day). Diapers were washed with a mild soap and rinsed thoroughly. Diapers were changed usually within one-half hour after soiling except during sleep. In the intertrigo study, 2 groups of 50 infants each were tested: (1) One group using methylbenzethonium chloride-corn starch dusting powder showed 92 percent cleared, and (2) the other group using only a corn starch powder control showed 84 percent cleared. In the ammonia dermatitis study, 2 groups of 50 infants each were tested: (1) One group using methylbenzethonium chloride-corn starch dusting powder showed 78 percent cleared, and (2) the other group using only a commonly used corn starch powder for the control showed 46 percent cleared.

Lipschutz and Fischer (Ref. 16) also evaluated methylbenzethonium chloride in a water miscible ointment for the treatment of ammonia dermatitis. One hundred infants were studied over a 3-month period. Infants were alternately treated with methylbenzethonium chloride ointment or the base without the active ingredient. In all cases the ointment was applied after each diaper change and on retiring for the night (an average of 7 times a day). Two groups of 50 infants each were tested: (1) One group using methylbenzethonium chloride ointment showed 82 percent cleared, and (2) the other group using ointment based control showed 42 percent cleared.

Although these studies (Refs. 14 and 16) were apparently well-controlled, they also suffer from defects. For example, in the Bleier and Niedelman study (Ref. 14) ammonia dermatitis was not defined, and the time until cure was not specified. In the Lipschutz and Fischer study (Ref. 16), the severity of the rash in each group was not indicated. In addition, in both of the above studies (Refs. 14 and 16), cleansing methods, such as exposure to soap and water, were not specified. Bleier and Niedelman simply state that "cleansing and attention to diaper changes were observed as usual." Lipschutz and Fischer state that "routine skin and diaper care was observed." Thus, these studies are not adequate to specifically evaluate the effect of residual soap or detergent on infant's skin on the activity of methylbenzethonium chloride.

Furthermore, neither Bleier and Niedelman (Ref. 14) nor Lipschutz and Fischer (Ref. 16) address the issue of bacterial involvement in diaper dermatitis or confirm the presence of ammonia or ammonia-forming bacteria on the skin either before or after therapy. While the data indicate that methylbenzethonium chloride may possibly be effective in the prevention or treatment of diaper rash, more information is needed before it can be placed in Category I for this use. The agency believes that further in vivo bacteriological studies are needed; specifically in vivo studies in infants to demonstrate the effect of the antibacterial activity of methylbenzethonium chloride on the skin flora and whether this effect correlates with clinical improvements in the diaper rash. Also bacteriological studies are needed to show that the long-term use of methylbenzethonium chloride does not result in potentially harmful changes in the normal flora of the skin in the diaper area.

The agency is concerned about the safety and effectiveness of antimicrobials being used regularly in the diaper area and whether such chronic use and the concomitant alteration of the dermal ecology could even aggravate diaper dermatitis.

Accordingly, the agency is classifying the quaternary ammonium compounds benzalkonium chloride, benzethonium chloride, and methylbenzethonium chloride for use in diaper rash drug products in Category III for both safety and effectiveness. (See also comments 5 and 6 above.)

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12. One manufacturer submitted data and information (Ref. 1) for two products (tablets and granules) containing methylbenzethonium chloride used as a final rinse to impregnate diapers. The tablets contained 12.7 percent methylbenzethonium chloride and the granules contained 6 percent methylbenzethonium chloride per teaspoon. The directions for preparing the diaper rinse stated one tablet or one level teaspoon of granules should be dissolved in 2 quarts of water for six diapers (or the equivalent of one pound in diapers). The products were labeled as an antibacterial diaper rinse and contained the following labeling claims: "Eliminates cause of diaper rash (ammonia dermatitis)," "* * * eliminates the cause of diaper rash by checking formation of urinary ammonia in wet diapers up to fifteen hours despite repeated wettings. Note absence of ammonia odor," "For ordinary protection, rinsing the night diapers with * * * is considered sufficient, when this is inadequate, rinsing of day diapers as well is recommended in addition to frequent diaper changes," and "As an added precaution against ammonia diaper rash, rinse baby's clothing and crib sheets with * * * ."

Data also were submitted for a commercial diaper rinse solution containing 25 percent methylbenzethonium chloride, 8.5 percent alcohol, and 0.8 percent trisodium ethylenediamine tetraacetate.[1] The directions for diluting the rinse solution to obtain 1 ounce per 100 pounds dry weight ranged from 1 ounce of rinse solution to 30 gallons of water for a 100 pound dry load of diapers to 5 ounces of rinse solution to 90 gallons of water for a 500 pound load. The labeling of this product stated that it "Eliminates cause of ammonia dermatitis."

The manufacturer contended that methylbenzethonium chloride released from impregnated diapers can effectively and safely ameliorate and prevent certain forms of diaper rash. The drug presumably acts by killing the microorganisms in urine and feces that produce ammonia and other (as yet, unspecified) irritating agents. The company contended that, on the basis of its submitted clinical studies, a 1:25,000 dilution of methylbenzethonium chloride should be classified in Category I as a diaper rinse.

As discussed in comment 4 above, the agency considers diaper rinse products with diaper rash claims to be drugs. As discussed in comment 11 above, the diaper rinse products are being evaluated separately from topical dosage forms containing methylbenzethonium chloride. As stated in comment 11, the agency did not concur with the NAS–NRC conclusion (Ref. 2) concerning the efficacy data in the NDA for methylbenzethonium chloride diaper rinse. Moreover, the NAS-NRC Panel's original evaluation of "effective but * * *" was changed to "possibly effective" in the DESI evaluation published in the Federal Register of July 3, 1971 (36 FR 12705). As discussed in comment 11 above, the agency concluded that data were needed to show efficacy against all the organisms that can produce ammonia. Also, efficacy needed to be demonstrated under use conditions. The agency also had concern that the labeling for the diaper rinse product did not caution that the antiseptic action of methylbenzethonium chloride can be altered by anionic detergents, including soap. The agency required data showing that methylbenzethonium chloride rinse is effective when used on diapers washed with anionic detergents or soaps even though the diapers are rinsed thoroughly before the diaper rinse is applied.

The effectiveness of a final diaper rinse containing methylbenzethonium chloride is based on the theory that "the positively charged functional portion of the quaternary molecule is attracted to and substantive to negatively charged fabric; it may be applied to the fabric from a quaternary solution by rinsing, padding, or spraying," (Ref. 3). Jenkins (Ref. 4) noted that when a quaternary ammonium fabric softener is added to the rinse water the cationic surfactant adheres to the fabric, surrounds its fibers, and acts as a lubricant so that the individual fibers are able to move freely, relative to each other, with the result of the material feeling soft. Jenkins also noted that quaternary ammonium surfactants have bacteriostatic activity and that some researchers had reported that treating diapers with fabric softeners tends to decrease both the incidence and exacerbation of diaper rash.

The agency believes that the following in vitro bacteriological studies on impregnated diapers indicate that the methylbenzethonium chloride final rinse is not inactivated by residual soap in clean-laundered fabric, and may maintain antibacterial activity in soiled diapers as well. The manufacturer submitted several studies (Refs. 5 through 15), in which in vitro tests were conducted on the antibacterial activity of fabrics impregnated with methylbenzethonium chloride, and on the use of methylbenzethonium chloride

[1] The agency has determined that the name "edetate trisodium" is the appropriate name for this ingredient.

soaks on soiled diapers. Lawrence and Maffia (Ref. 5) reviewed the literature in 1957 on the antiseptic impregnation of contaminated fabric (sick-room, diapers, etc.) and concluded that the quaternary ammonium compounds apparently were the most successfully used antiseptics in fabric impregnation because (1) with proper care they are nonirritating, nonallergic, nontoxic, and are adequate antibacterial agents, and (2) they tend to remain in the fabric despite many washings. The authors noted that washing cottons treated with quaternary ammonium compounds in cold, warm, or boiling water fails to remove the antibacterial properties of the textile. The authors concluded that washing with an anionic surface-active agent (true soaps, synthetic soaps) will, however, destroy the bactericidal properties of the quaternary ammonium compounds contained in the impregnated cloth.

In 1963, Lawrence (Ref. 6) compared two commercially available antibacterial diaper impregnation agents, methylbenzethonium chloride and neomycin sulfate. Several tests were carried out at various dilutions of the two agents, under laboratory conditions, under actual commercial laundry conditions, and on untreated "soiled" diapers. In one agar plate inhibition test, small sections of commercially-laundered diapers impregnated with methylbenzethonium chloride were tested with agar cultures of *B. ammoniagenes* or *S. aureus*. The methylbenzethonium chloride diffused into the agar from the fabric to produce a zone of inhibition around the diaper patches. Lawrence (Ref. 6) also tested untreated soiled diapers following the normal practice of first rinsing the feces from the fabric in a flush toilet. The diapers were still stained with fecal material and were kept at room temperature for 3 days. One diaper was then soaked in 2,000 mL of a 1:8,000 methylbenzethonium chloride diaper-soak; no organisms could be recovered from the solution after 1 hour. Lawrence concluded that the product containing methylbenzethonium chloride appears to remain the antibacterial agent of choice for impregnation of fabrics with minimal danger of patient sensitization and no reported incidences of the production of bacteria with increasing resistance to this germicide.

Soren (Ref. 7) used three dilutions of methylbenzethonium chloride to wash soiled diapers from hospital pediatric wards. Various in vitro tests were conducted on the diapers after washing in "Tide" detergent and rinsing in methylbenzethonium chloride (1:14,000, 1:9,500, and 1:7,000) final rinse to determine the presence of coliform bacteria, ammonia-forming bacteria, total bacterial count, and residual antiseptic properties in inhibiting *B. ammoniagenes*, *S. aureus*, and ammonia. Soren concluded that a 1:7,000 concentration of methylbenzethonium chloride in 3 quarts of water should be used as a rinse for each six diapers laundered in home automatic washing machines.

These studies demonstrate that final diaper rinses containing methylbenzethonium chloride do remain in the diaper and provide effective in vitro bacteriostatic activity provided they are used according to directions that alert the consumer not to mix anionic detergents, including soap, with these diaper rinses. However, the agency does not consider these data as sufficent to establish effectiveness for the treatment of diaper rash. As discussed above (see comment 2), it was noted that Cooke's ammonia theory of diaper rash has been questioned by more recent studies. Therefore, any claims concerning this ammonia theory need to be supported by clinical studies on infants. Such studies must include bacteriological studies to correlate a reduction in ammonia-producing bacteria with a clinical improvement in the diaper rash (see comment 2 above). Thus, in vitro tests alone on impregnated diapers are not sufficient to prove effectiveness for diaper rash.

The agency has evaluated the clinical studies (Refs. 14 through 18) submitted by the comment, including those (Refs. 14, 15, and 16) that were cited by the NAS–NRC Panel (Ref. 2), in which methylbenzethonium chloride was used as a final diaper rinse to treat or prevent diaper rash in infants. Most of these studies were conducted in the late 1940's to early 1960's, and frequently these studies were not controlled or involved a skin care regimen that included topical preparations in combination with the impregnated diapers. Benson et al. (Ref. 14) reported on 50 infants ranging in age from 1 to 18 months who were treated for moderate to severe ammonia dermatitis with diapers impregnated with methylbenzethonium chloride. Mothers were instructed to use 1 tablet in 2 quarts of water (approximately a 1:25,000 dilution) to impregnate up to six washed diapers. When the infants were observed at 3 days, 31 infants were improved, 18 were cleared, and one had no response. At 7 days, 49 were cleared and one still had no response. After stopping treatment, 14 infants returned in 2 to 4 weeks with a mild ammonia dermatitis which responded to retreatment with the impregnated diapers. The authors stated that many of the mothers noted that they no longer smelled ammonia in the diaper after treatment. Benson et al. (Ref. 15) later reported on 500 cases of mild, moderate, or severe ammonia dermatitis; 436 cleared within 1 week of treatment with methybenzethonium chloride impregnated diapers. The authors also stated in this second study that severe cases of ammonia dermatitis had been secondarily infected with *S. aureus* and various streptococci in which triple strength impregnated diapers (3 tablets to 2 quarts of water) gave the best results. However, the agency notes that both of these studies by Benson et al. (Refs. 14 and 15) were uncontrolled and did not give adequate details about the bacteriological skin counts or the methods used to cleanse the infants. The agency does not consider these studies adequate to demonstrate effectiveness.

Lipschutz and Agerty (Ref. 16) studied 170 institutionalized children from 2 months to 2½ years of age plus 30 children from private practice. The skin care regimen included daily bathing of each child with detergent skin cleanser containing hexachlorophene 0.5 percent, use of a methylbenzethonium chloride (1:1,800) corn starch base powder after each bath and diaper change, and use of a methylbenzethonium chloride cream or ointment (1:1,000) in the event of diarrhea or loose stools. The diapers and layette garments were impregnated with methylbenzethonium chloride (1:9,500) rinse solution. Four percent of the children on this prophylactic regimen developed a skin condition. The authors compared these results to an earlier control series of 100 cases over a comparable period in which only soap and water were employed prophylactically and the incidence of skin conditions was 29 percent. However, no further details were given concerning this control group, which apparently did not include vehicle controls. Because of the manner in which the study was conducted, the agency cannot determine which component(s) contributed to the benefit observed: the methylbenzethonium chloride in the impregnated diapers, the methylbenzethonium chloride in the topical preparations, the other antimicrobial (hexachlorophene), or the skin protectant ingredients in the topical preparations.

The study by Lipschutz and Fischer (Ref. 17), in which they evaluated the use of methylbenzethonium chloride-rinsed diapers for the treatment of ammonia dermatitis in infants 3 months to 2 years of age, indicates that this

method of using methylbenzethonium chloride may be of benefit for diaper rash. Three groups of 50 infants each were treated with a methylbenzethonium chloride (1:1,800) corn starch base dusting powder. The treatment of the diapers for the three groups differed: group 1 used diapers laundered with a mild soap and rinsed thoroughly, and the diaper rash cleared in 78 percent; group 2 used only night diapers rinsed in methylbenzethonium chloride, and the diaper rash cleared in 94 percent; and group 3 used all diapers rinsed in methylbenzethonium chloride, and the diaper rash cleared in 98 percent. A fourth group of 50 infants serving as an untreated control was treated only with a commonly used corn starch powder and with untreated diapers laundered only with a mild soap and rinsed thoroughly. The diaper rash cleared in 46 percent of the infants.

As discussed above in comment 11, the Lipschutz and Fischer studies suffer from a number of defects. For example, the severity of the rash in each group was not indicated, and the cleansing methods, such as exposure to soap and water, were not specified. The authors simply state that "routine skin and diaper care was observed." Also, the concentration of the methylbenzethonium chloride in the diaper rinse was not stated. It appears that the tablet dosage form submitted by the comment was used, presumably at the labeled directions of 1 tablet in 2 quarts of water for 6 diapers (1:25,000 dilution). The agency finds that although the Lipschutz and Fischer study showed that the methylbenzethonium chloride diaper rinse may have contributed to lowering the incidence of diaper rash, the diaper rinse was not tested separately from the methylbenzethonium chloride powder. Therefore, this study is not adequate to establish that methylbenzethonium chloride in a diaper rinse alone would be effective to treat or prevent diaper rash.

As discussed in comment 11 above, the data indicate that methylbenzethonium chloride may possibly be effective in the prevention or treatment of diaper rash. However, before this ingredient can be placed in Category I for this use, further in vivo bacteriological studies are needed, specifically in infants to demonstrate the effect of the antibacterial activity of methylbenzethonium chloride on the skin flora and whether this correlates with clinical improvements in diaper rash. None of the clinical studies (Refs. 14 through 18) discussed above addresses the issue of bacterial involvement in what they describe as ammonia dermatitis. Also, the proper effective concentration of methylbenzethonium chloride rinse needs to be determined. While the company stated that a 1:25,000 dilution was effective, some of the submitted studies (Refs. 6, 11, and 17) were conducted using stronger concentrations of 1:9,500 or less dilutions. Therefore, the agency is classifying methylbenzethonium chloride for use as a diaper rinse in Category III.

References

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

(18) Meadows, R.W., "Pediatric Skin Care—A Prophylactic Study," *Western Medicine*, 6:47–51, 1965.

13. Data (Ref. 1) were submitted for two products containing methylbenzethonium chloride with claims for treating and preventing infant diaper rash and similar conditions in older persons having poor bowel and bladder control. Additional data (Ref. 2) contained studies on the use of methylbenzethonium chloride in various dosage forms for skin care of incontinent, chronically ill, or geriatric patients.

The agency discussed the use of topical dosage forms and diaper rinses containing methylbenzethonium chloride in the treatment and prevention of diaper rash in infants and children in comments 11 and 12 above. In this comment, the agency discusses the use of topical products and fabric-impregnating final rinse dosage forms containing methylbenzethonium chloride for incontinent adult patients with skin problems similar to diaper rash.

The submitted studies (Refs. 3 through 11) include reports of the clinical use of various methylbenzethonium chloride products on 632 adult incontinent patients with no side effects noted. However, the agency does not consider these reports to be adequate safety data. The safety of methylbenzethonium chloride for use in infants and children is discussed in comment 11 above and the conclusion reached there (Category III) is applicable to the use of methylbenzethonium chloride in incontinent adults.

Also, as discussed in comment 11 above, the NAS–NRC Panel on Drugs Used in Dermatology II evaluated an ointment product and a diaper rinse product containing methylbenzethonium chloride. That Panel categorized both products as "effective but * * *" and cited several articles (Refs. 3 through 6) concerning skin care of adult or elderly incontinent patients. The agency did not concur with the NAS–NRC Panel, and in the **Federal Register** of July 3, 1971 (36 FR 12705), the agency classified these products as "possibly effective" in

preventing diaper rash and eliminating the cause of diaper rash (ammonia dermatitis). The agency concluded at that time that the manufacturer needed to demonstrate (1) efficacy against all the organisms that can produce ammonia, (2) efficacy under use conditions, and (3) that antibacterial activity still occurred when topical products were applied to detergent- or soap-washed skin or when fabrics that had been laundered with detergent or soap were treated with a fabric rinse containing methylbenzethonium chloride. These concerns applied equally to products containing this ingredient used on adults or children.

With respect to the antibacterial activity of methylbenzethonium chloride against ammonia-producing organisms in adult incontinents, the agency notes that Nagamatsu, Johnson, and Silverstein (Ref. 3) reported on the use of methylbenzethonium chloride impregnated dressings, diapers, or towels in 23 incontinent patients, aged 39 to 75 years, for prophylaxis or for treatment of skin excoriation. (This uncontrolled study is discussed in comment 11 above.)

Silverstein and Gips (Ref. 4) studied 11 incontinent patients ranging in age from 56 to 95 (median age 80 years) with skin graded according to the severity of the lesions, as follows: grade 0—no lesions, grade I—erythematous, edematous skin, grade II—superficial ulceration, and grade III—deep ulceration. All patients wore diapers impregnated with a 1:12,000 solution of methylbenzethonium chloride; the diapers were changed 6 to 8 times daily. At the discretion of the nurses, methylbenzethonium chloride powder (1:1,000 in corn starch and sodium bicarbonate) was applied to the interior of the diaper. Where actual ulceration was present, methylbenzethonium chloride 1:1,000 ointment was applied. Patients were observed on this therapy from 8 to 231 days (with a median study period of 104 days) with the following results: (1) Four patients without lesions (grade 0) continued to have good skin condition; (2) four patients with grade I or II lesions were cured in a median of 40 days, and on withdrawal of the ointment, the skin remained in good condition with the prophylactic use of the powder and impregnated diapers, (3) of the three patients with grade III ulceration—one patient had no significant lesions after 90 days (with the skin area in excellent condition at the end of 119 days when the patient died), one patient improved, with lesions upgraded to superficial ulcerations at 21 days (which was the end of the study period) while the third patient showed initial improvement but died before treatment was completed. Although this treatment phase was not controlled, eight of the patients were subsequently taken off the methylbenzethonium chloride regimen and continued in an untreated control phase for 62 days that consisted of their usual nursing care and untreated diapers. Four of the patients also received drying powders which did not contain significant amounts of antiseptics. During the untreated control phase, the severity of the lesions of seven of the eight patients changed from a grade 0 to I classification to a I or II classification. After this control period, the patients were then put back on methylbenzethonium chloride impregnated diapers solely for 28 days, after which all patients had clear skin. The authors noted that the nursing staff consistently reported the presence of ammoniacal odor a day or two after the discontinuance of the use of the treated diapers. The reports of the odor ceased upon resuming the use of the treated diapers.

Smigel (Ref. 5) treated 57 incontinent patients age 48 to 91 years (average age 75½ years) who had skin pathology due primarily to ammonia dermatitis, or secondarily aggravated by it. The skin pathology was classified in five degrees of severity: group A—erythema, group B—excoriations, group C—vesicles and pustules, group D—superficial ulcerations, and group E—deep ulcerations. All patients were treated with methylbenzethonium chloride rinsed linen and methylbenzethonium chloride powder used by rubbing it into the bed clothes rather than dusting it on the skin. More severe cases (half of group B, and all of groups C, D, and E) were also treated by application of methylbenzethonium chloride ointment. In all but 2 of the 57 patients, "urinary skin lesions" were either improved or completely healed; and a marked decrease in the usual offensive odor was noted. Although the treatment phase of the study was uncontrolled it was followed by a controlled prophylactic phase for 40 of the healed patients, in which 20 patients were continued on methylbenzethonium chloride rinsed linen and powder, and 20 were taken off the treatment ("controls"). After 4 weeks, recurrences to the first 3 degrees of skin pathology were noted in 11 (55 percent) of the controls and only in 2 (10 percent) of the patients who continued to receive the treatment. Although the author did not state the concentration of methylbenzethonium chloride in the various dosage forms, the trade products used were mentioned. The methylbenzethonium chloride concentrations in these products are 1:1,000 in the ointment, 1:1,800 in the powder, and 1:25,000 use concentration for the diaper rinse tablets.

Lawrence and Silverman (Ref. 6) reported on the effects of the use of prophylactic and therapeutic medications and appropriate supportive measures to prevent or treat skin problems of 111 bedridden, incontinent, geriatric patients. The patients were rotated through three 60 day phases of skin care: (I) normal hospital skin care and usual hospital laundry facilities; (II) normal hospital skin care and linens treated with methylbenzenthonium chloride solution; and (III) skin care with cream, powder, and lotion containing methylbenzethonium chloride, Ivory soap for bathing, and linen treated as in phase II. All linens for the hospital were washed in the laundry according to the standard laundry routine and were used for the phase I control. The linens used in phases II and III were treated by adding methylbenzenthonium chloride solution in a ratio of 2 ounces per 100 pounds of dry weight of linen in the final rinse for a period of 5 minutes. Laboratory examination of the treated fabric and control laundered fabric showed a decrease in the presence of bacteria in the treated fabric and demonstrated that patches of the treated fabric could inhibit the growth of *S. aureus* in an agar plate inhibition test. The agency believes that these results support the agency conclusions, in comment 12 above, that trace residual soap or detergent in previously laundered and rinsed fabric does not inactivate a subsequent final rinse containing methylbenzenthonium chloride and allows the ingredient to provide effective in vitro bacteriostatic activity.

This study (Ref. 6) was carried out on three 43-bed wards using the following 60-day rotation schedule: Ward A, phases I to III to II; ward B, phases II to I to III; and ward C, phases III to II to I. All patients were observed at 2-week intervals for ammoniacal or perianal dermatitis, secondary infections, intertrigo, decubitus ulcers, dry skin, or other special problems. Dermatological problems in the pretest period involved 71 percent of the patients; these problems decreased with the addition of methylbenzethonium chloride treatment as follows: Phase I, 62 percent; phase II, 21 percent; Phase III, 15 percent. At the post-test period (2 weeks following termination of the program), problem skin was observed in 56 percent of the patients, which the authors felt suggested a residual antiseptic effect.

The authors concluded that, even though the effect of methylbenzethonium chloride dermatologic products without treated linen was not studied, the results demonstrated the effectiveness of a prophylactic program in the care of bedridden, incontinent, convalescent, or geriatric patients. However, the agency notes that diagnoses of skin abnormalities prior to treatment and observations of the skin during the study were made by a single nonqualified observer, and that no bacteriological skin counts were done.

The agency finds that these studies seem to indicate that the impregnation of patient clothing, diapers, and bed linens with methylbenzethonium chloride could result in the reduction of the incidence of skin dyscrasias in long-term bedridden, incontinent patients and that the use of the methylbenzethonium chloride topical preparations may have contributed an additional benefit. The agency believes that these studies also appear to indicate that the effect any residual anionic soap on the skin would have on the antibacterial activity of methylbenzethonium chloride would be minimal. This finding is supported by the Lawrence and Silverman study (Ref. 6) which showed that the most significant improvement was in phase III of the study where it was specifically stated that Ivory soap (a known anionic soap) was used to bathe the patients. However, no bacteriological studies were done to confirm this. Therefore, the agency concludes that further data, particularly bacteriological skin counts, are needed to resolve the issues raised by the agency at the time of the DESI review regarding possible lessening of antibacterial effectiveness of methylbenzethonium chloride by residual anionic soap on the skin. Furthermore, in the studies where the condition was diagnosed as ammonia dermatitis, no attempts were made to assay levels of ammonia or ammonia-forming bacteria on the skin or clothing either before or after therapy. Therefore, because no bacteriological skin counts were taken on the patients, further in vivo bacteriological studies, specifically in incontinent adults, are needed to demonstrate the effect of the antibacterial activity of methylbenzethonium chloride on the skin flora and whether this correlates with the clinical improvements in skin problems similar to diaper rash. Also, as noted above, safety aspects need to be resolved. Therefore, the use of methylbenzethonium chloride for the treatment or prevention of adult skin problems similar to diaper rash is classified in Category III.

References

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I. Comment on Oxyquinoline

14. One manufacturer submitted data (Ref. 1) to the Miscellaneous External Panel for a combination product that included 0.1 percent 8-hydroxyquinoline and 0.05 percent 8-hydroxyquinoline sulfate with labeling claims for "diaper rash—acts as an antiseptic to help fight staph germs and other bacteria." The submission stated that confirmation of the antibacterial activity of hydroxyquinoline (or oxyquinoline) was substantiated in the medical and biological literature. A subsequent submission (Ref. 2) included reports providing additional data confirming the contribution of hydroxyquinoline in the combination product to the retardation of bacterial growth, although this demonstrated activity was insufficient to prevent ammonia formation. Other investigations in the submission showed that the antibacterial activity of the final formulation was directly related to another antimicrobial ingredient (boric acid) and that the activity of the hydroxyquinolines was shown to be diminished in the presence of the Zn^{++} ion from the zinc oxide in the formulation. A later submission (Ref. 3) from the same manufacturer stated that the hydroxyquinolines were included in the formula to provide the characteristic fragrance of the product in accordance with FDA's proposed rule for general conditions for use and labeling of inactive ingredients (April 12, 1977; 42 FR 19156). This submission also included revised labeling for this product which did not include any claims of antimicrobial activity.

In the "USAN and USP Dictionary of Drug Names" (Ref. 4), 8-hydroxyquinoline is designated as oxyquinoline and 8-hydroxyquinoline sulfate is designated as oxyquinoline sulfate. The Antimicrobial II Panel, the Vaginal Panel, and the Oral Cavity Panel classified the oxyquinolines as Category III for various OTC topical uses. The concentrations of the oxyquinolines reviewed by these panels were in the same range as the combination product labeled for diaper rash that was submitted to the Miscellaneous External Panel.

The Antimicrobial II Panel recommended that benzoxiquine, oxyquinoline, and oxyquinoline sulfate could be used alone or in combination to equal a total oxyquinoline concentration of 0.06 to 2.5 percent for the treatment of athletes foot, jock itch, and ringworm but placed these ingredients in Category III, concluding that there are insufficient data available to classify them as Category I for safety or effectiveness (47 FR 12540). The Vaginal Panel recommended that oxyquinoline citrate or oxyquinoline sulfate, used as a vaginal douche at a concentration of 2 percent for the relief of minor irritations of the vagina, be placed in Category III because the data are insufficient to prove safety or effectiveness for this use (48 FR 46715 to 46716). The Oral Cavity Panel reviewed the topical use of oxyquinoline sulfate at a 0.1-percent concentration in aqueous solution in the form of a rinse, gargle, or spray on the mucous membranes of the mouth and throat, not more than 3 or 4 times daily (47 FR 22881). The Panel concluded that the data available were insufficient to permit final classification of safety and effectiveness and placed the ingredient in Category III.

Based on the above and the historical usage of oxyquinoline as an active ingredient, the agency questions whether a total oxyquinoline concentration of 0.15 percent can be considered an inactive ingredient. A final determination of the status of oxyquinoline has not been made in any of the above-referenced rulemakings.

In the proposed rule concerning inactive ingredients (42 FR 19156 at 19157), the agency stated the following:

Various OTC drug panels have questioned whether an OTC drug may retain as an inactive ingredient an ingredient that was formerly listed as an active ingredient, but which was found not to be generally recognized as safe and effective (Category II) or to require additional testing (Category III). If these ingredients have been promoted by manufacturers for an extended time, there is a potential for misleading consumers if the general recognition of the safety and effectiveness issue is unresolved and the name of the ingredient is retained on the label or in the labeling with an unwarranted degree of prominence. The Commissioner believes this should not be permitted, and this proposal is intended to preclude the retention and redesignation of an active ingredient as an inactive ingredient unless it serves an acceptable function as an inactive ingredient. As a result, manufacturers of OTC drug products containing an ingredient in Category II or Category III shall, at the end of the time period permitted for marketing, or if found to require further testing before a determination as to general recognition of safety and effectiveness can be made for such ingredients, be required by the effective date either to reformulate the product to remove the ingredient or if it is retained in the product as an inactive ingredient, to establish that the ingredient fulfills the requirements for use as an inactive ingredient in the product.

This proposal states that "fragrances" are one of the acceptable categories for inactive ingredients (42 FR 19156 at 19160). The agency has no information that the oxyquinolines are necessary as fragrances, as defined in § 330.3(h) of the proposal, for use in OTC diaper rash drug products. The agency invites information and comments on (1) the use of oxyquinolines as fragrances in OTC diaper rash and related drug products and (2) the minimum concentration of oxyquinoline needed to achieve a fragrance effect.

Based on the above, the agency is classifying all oxyquinolines for use in diaper rash drug products in Category III for both safety and effectiveness, and is inviting the submission of additional information on their use as fragrances in such drug products.

References

(1) OTC Volume 160077.
(2) OTC Volume 160091.
(3) Comment No. C00163, Docket No. 75N-0183, Dockets Management Branch.
(4) Heller, W. M., editor, "USAN and the USP Dictionary of Drug Names," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 418, 1990.

J. Comment on P-Chloromercuriphenol.

15. One manufacturer submitted information to the Miscellaneous External Panel (Ref. 1) and the Antimicrobial II Panel (Ref. 2) for a product labeled as containing parachlormercuriphenol [1] in a hydrated base of lanolin with petrolatum, yellow wax, sodium borate, and aromatic oils with labeling that included claims for the treatment and prevention of diaper rash. The manufacturer subsequently notified the agency that the product is no longer marketed and withdrew the submissions (Ref. 3).

Although the Miscellaneous External Panel did not review this product specifically for its diaper rash claims, in another OTC drug rulemaking proceeding, that Panel classified all mercury compounds in Category II for topical antimicrobial use, citing problems associated with the safety of some and with the efficacy of all compounds (January 5, 1982; 47 FR 436). The Panel was unable to locate nor was it aware of any data demonstrating the safety and effectiveness of p-chloromercuriphenol when used as an OTC topical antimicrobial active ingredient and, without further discussion, the Panel classified it as Category II for this use (47 FR 436 at 438).

Toxicity from cutaneous mercury therapy has been reported since 1923 (Ref. 4). As noted by the Contraceptive Panel (45 FR 82014 at 82036), data indicated that at least two organic mercury compounds, phenylmercuric acetate and phenyl-mercury-dinaphtylmethane sulfonate, can be absorbed through the skin (Refs. 5 and 6). That Panel also noted that administration of calomel has caused specifically in infants a severe febrile (erythematous) disease known as acrodynia (pink disease) (Refs. 7, 8, and 9). While many cases of acrodynia have been attributed to orally ingested mercury in teething powders, the agency notes that there have been reports of acrodynia resulting from topical treatment of diaper rash with mercury containing ointments or diaper rinses (Refs. 10, 11, and 12).

In addition to concerns about mercury poisoning, the agency notes that p-chloromercuriphenol is a phenol derivative. Phenol (see comment 16 below) and phenol derivatives, such as hexachlorophene (see comment 10 above) and resorcinol (see comment 17 below), have also caused severe systemic toxicity, including death, in infants when applied externally. The agency believes that particular caution is needed when considering the use of any phenolic compound in infants.

There is a lack of toxicity data specific to p-chloromercuriphenol. However, in light of the above concerns about mercurials and phenolic compounds in general and in view of the two Panels' recommendations discussed above, the manufacturer's withdrawal of its submissions, and the fact that no other data were submitted on this ingredient, the agency is classifying p-chloromercuriphenol and all other mercury compounds in Category II for the treatment and prevention of diaper rash.

References

(1) OTC Volumes 160025, 160221, and 160235.
(2) OTC Volume 070007.
(3) Letters from H. Jenkins, Creomulsion Company, to W.E. Gilbertson, FDA, dated February 3, 1987 and June 13, 1988, in OTC Volume 02DTFM, Docket No. 75N-183D, Dockets Management Branch.
(4) Kahn, G., "Three Thousand Years of Mercury—A Plea for Abandonment of a Dangerous, Unproven Therapy," *Cutis*, 6:537-542, 1970.
(5) Skerfving, S., "Organic Mercury Compounds—Relation Between Exposure and Effects," *in* "Mercury in the Environment," Edited by Friberg, L., and J. Vostal, The CRC Press, Cleveland, pp. 141-168, 1972.
(6) Goldberg, A.A., M. Shapero, and E. Wilder, "The Penetration of Phenylmercuric Dinaphtylmethane Disulphonate Into Skin and Muscle Tissue," *Journal of Pharmacy and Pharmacology*, 2:89-97, 1950.
(7) Barrett, F.R., "Calomel and Pink Disease: Preliminary Report," *The Medical Journal of Australia*, 44:714-716, 1957.
(8) Barrett, F.R., "A Biochemical Approach to Calomel-Induced Mercurialism and to the Aetiology of Pink Disease," *The Medical Journal of Australia*, 44:242-245, 1957.
(9) Jones, F.A., and E.W. Godding, "Management of Constipation," Blackwell Scientific Publication, London, p. 55, 1972.
(10) McCoy, G.E., "Acrodynia Following the use of Bichloride of Mercury Diaper Rinse—Report of Two Cases," *Journal of the Indiana State Medical Association*, 43:1095-1097, 1950.
(11) Rajagopal, C., and D. Hamilton, "Clinical Curio: Pink Disease is Not Dead," *British Medical Journal*, 288:705, 1984.
(12) Warkany, J., and D.M. Hubbard, "Mercury in the Urine of Children with Acrodynia," *The Lancet*, 1:829-830, 1948.

K. Comment on Phenol

16. One manufacturer submitted data (Refs. 1 and 2) to the Miscellaneous External Panel for two products, an ointment containing 0.16 percent phenol and a liquid containing 0.55 percent liquified phenol, in combination with various other active ingredients. The liquid preparation was labeled for "chafing" and "heat rashes and ordinary

[1] The agency has determined that the name "p-chloromercuriphenol" is the preferred name for this ingredient.

infant irritations" (Ref. 1). The ointment preparation was labeled "* * * helps prevent infection of * * * chafing, * * *," and "Relieves itching that accompanies many skin conditions such as common rashes, prickly heat, * * *" (Ref. 2). Although neither product was specifically labeled for use on infants or for diaper rash, the submitted data (Ref. 2) included a study on an ointment containing a combination of active ingredients that included 0.2 percent phenol in the management of diaper dermatitis in 20 infants, ages 5 weeks to 30 months. However, the study was a comparison of the total formulation compared to the total formulation with aloe active principle added. The study does not provide any information on the contribution of the phenol in the product to the results obtained.

Phenol has been reviewed for safety for topical, oral, and vaginal use in a number of OTC drug rulemakings. Phenol at concentrations greater than 1.5 percent (except in a special formulation with camphor) has been placed in Category II for safety in all rulemakings. Phenol at concentrations of 1.5 percent or less has received varying recommendations from different panels.

The Antimicrobial I Panel placed phenol at 1.5 percent or less in Category III for all antiseptic uses (September 13, 1974; 39 FR 33102 at 33133). That Panel was particularly concerned about the safety of using phenol in infants and recommended the warning: "Not to be used on infants under 6 months of age." The Panel noted that phenol is metabolized and eliminated from the body by glucuronide conjugation in the liver and there is a reported deficiency of metabolic conjugating mechanisms in infants. The Panel recommended that a toxicological evaluation of phenol should include studies to demonstrate safety in young animals deficient in these detoxification mechanisms and stated that because the liver is considered the major organ for conjugating, the effect of inadequate or impaired liver function on elimination and toxicity should also be determined.

The Panel was further concerned about the reports of local and systemic toxicity occurring after phenol-containing products had been applied over large areas of the body and covered with bandages. The Panel recommended that the use of phenol be restricted to small areas of the skin and that occlusive dressings, bandages, or diapers in any form should not be used. The Panel specifically concluded that phenol-containing preparations should not be used for the treatment of diaper rash, and recommended the following labeling: "Warning: Do not use for diaper rash or over large areas of the body or cover the treated area with a bandage or dressings," (39 FR 33133).

In the tentative final monograph for OTC antimicrobial drug products (January 6, 1978; 43 FR 1210), the Commissioner affirmed the conclusions of the Antimicrobial I Panel that phenol should not be used in infants until additional safety studies are conducted. The agency proposed a warning not to use phenol-containing products on infants under 6 months of age unless such studies are conducted (43 FR 1237 to 1238). The Commissioner also affirmed the Panel's conclusions that phenol-containing preparations should not be used for the treatment of diaper rash and should have a label stating "Warning: Do not use for diaper rash * * *." (43 FR 1238). The Commissioner further concluded that phenol may be used as an inactive ingredient for its aromatic characteristics in formulations in concentrations of less than 0.5 percent of phenol in a free state.

The Topical Analgesic Panel placed phenol 0.5 to 2 percent in Category I for use as an external analgesic (44 FR 69768 at 69832; December 4, 1979). However, in discussing the uses of topical drugs in infants (44 FR 69773 and 69774), the Panel stated: "The effects of occlusion from a diaper, lying on a waterproof mattress, wet clothing, or from body folds touching each other can cause disease and enhance cutaneous penetration of medicaments * * *. The Panel is concerned about the effects of a high local concentration of a drug on the integument itself under the occlusive conditions which exist in infants. Ingredients under occlusion may possibly be corrosive to the infant's skin. Biologic systems which metabolize and excrete drugs absorbed through the skin may not be fully developed in children less than 2 years of age." The Panel concluded that "to provide an added margin of safety, the ingredients reviewed below are not to be used for children under the age of 2 years except on the advice of a physician." Furthermore, in its evaluation of phenol (44 FR 69832 and 69833), the Panel stated that "dressings or compresses saturated with solutions of phenol, even though dilute, may cause sloughing, and are not recommended. Preparations containing 1 to 2 percent phenol should be applied only to the smallest area needing treatment and should not be bandaged to prevent severe skin irritation." The Panel recommended the following warning for products containing phenol: "Do not apply this product to extensive areas of the body or under compresses or bandages." The agency does not believe that the Panel's Category I evaluation of phenol as an external analgesic applies to use in diaper rash products which would be used on infants and children under 2 years of age, under occlusive diapers, and over extensive areas of the infant's body because all these conditions were specifically excluded by the Panel in its recommendation of phenol as safe for OTC use.

The Antimicrobial II Panel in its report on OTC antifungal drug products (March 23, 1982; 47 FR 12480) classified phenol in Category II for OTC topical use in the treatment of athlete's foot, jock itch and ringworm (47 FR 12518). The Panel stated that it received no data on the effect of dilute solutions of phenol on broken skin such as might be the case with athlete's foot, jock itch, or ringworm. The Panel also noted that in most reports of toxicity from dilute solutions of phenol bandaging was necessary to produce severe local changes. The Panel was concerned that using phenol in athlete's foot and jock itch would be similar to using it under a bandage because the affected areas would be covered by clothing. The Panel mentioned the specific lack of controlled studies evaluating (1) the absorption from small areas of application to either broken or intact skin, (2) the local effects of wound healing, and (3) the potential for hypersensitivity or idiosyncratic reaction. The Panel concluded that the use of phenol for athlete's foot, jock itch, and ringworm is outdated, irrational, and potentially dangerous. The agency considers these safety concerns about the topical use of phenol for jock itch in adults equally applicable to its use for diaper rash in infants.

The agency has considered the above three Panels' safety evaluations of topical phenol and other data, as discussed below, and concludes that phenol is not safe for use on infants for OTC diaper rash drug products. The specific safety concerns are (1) potential risks for local toxicity to skin when used under occlusive diapers, (2) potential for hypersensitivity reaction or topical overdose from skin absorption resulting in acute systemic toxicity especially in infants, and (3) potential for subacute percutaneous absorption from repeated use resulting in chronic systemic toxicity.

Accordingly, the agency has reassessed its prior conclusion of allowing the use of phenol as an inactive ingredient for its aromatic characteristics when such use would be in a diaper rash drug product. There is

an insufficient benefit to be gained from such use considering the potential risks to the infant. Therefore, phenol should not be used in any concentration as an active or inactive ingredient in a diaper rash drug product.

Based on the above, the agency is classifying phenol in Category II for safety as an ingredient in diaper rash drug products or for any labeling claims for similar uses in infants such as rash, prickly heat, heat rashes, chafing, or ordinary infant irritations.

The agency is aware that phenol 0.5 to 1.5 percent (and phenolate sodium 0.5 to 1.5 percent) has been proposed as Category I as an external analgesic in the tentative final monograph for OTC external analgesic drug products (48 FR 5867). Such products are indicated for the temporary relief of itching associated with minor skin irritations and rashes * * * and must bear the warning "Do not apply over large areas of the body or bandage," (48 FR 5869). Because of the agency's concerns that products containing phenol should not be used for diaper rash, the agency intends in the final monograph for OTC external analgesic drug products to expand the above warning to also state "Do not use for diaper rash."

References

(1) OTC Volume 160059.
(2) OTC Volume 160060.

L. Comment on Resorcinol

17. Submissions to the Miscellaneous External Panel (Ref. 1) and to the Antimicrobial I Panel (Ref. 2) were made by two manufacturers for products containing a combination of ingredients that included resorcinol. One product contained 2 percent resorcinol and the other contained 3 percent resorcinol. These products were labeled for the treatment of a number of skin conditions, including diaper rash. One submission (Ref. 1) stated that resorcinol was used in the product as a strong antiseptic. The submission also stated that resorcinol chemically resembled phenol in both formula and therapeutics, and the phenol coefficient of resorcinol against typhoid bacillis or staphylococcus is 0.4. The other submission (Ref. 2) stated that one of the medical uses of the product was as an antiseptic. No other data were submitted on the use of resorcinol.

Resorcinol has been reviewed for safety for topical use in five OTC drug rulemakings. In the **Federal Register** of December 3, 1982, the Miscellaneous External Panel concluded that resorcinol was safe for use on the scalp (for controlling seborrheic dermatitis or psoriasis) because of the limited size of the area and the thickness of the skin (47 FR 54646 at 54668). However, the Panel stated that resorcinol resembles phenol in its physiologic properties and, therefore, should not be used over large areas of the body or on thinner skin because enough drug can be absorbed through the skin to cause systemic poisoning. In the **Federal Register** of March 23, 1982, the Antimicrobial II Panel concluded that 2 percent resorcinol is safe for OTC topical use in the treatment of acne provided it has the following warning: "Apply to affected areas only. Do not use on broken skin or apply to large areas of the body," (47 FR 12430 at 12460). In the **Federal Register** of March 23, 1982, the same Antimicrobial II Panel concluded that the higher concentration of 10 percent resorcinol was not safe for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm (47 FR 12480 at 12520).

In the **Federal Register** of December 4, 1979 (44 FR 69768), the Topical Analgesic Panel concluded that 0.5 to 3 percent resorcinol is safe for use as an external analgesic in adults and children 2 years of age and older but that the following warning was needed: "Do not apply this product to large areas of the body." The Panel noted that, although resorcinol is much less toxic than phenol, cases of poisoning have been reported, with some fatalities. The Panel cited an article by Cunningham (Ref. 3) who found eight cases (mostly in children) of resorcinol poisoning, six of which were fatal. (See 44 FR 69835.)

In the **Federal Register** of May 27, 1980, a majority of the Hemorrhoidal Panel found resorcinol safe for external use on adults in a 1 to 3 percent concentration as a keratolytic for the relief of itching (45 FR 35576 at 35665 and 35666). However, the Panel stated that the amount used must be limited because the toxicity of resorcinol is high. The Panel noted that resorcinol can be absorbed rapidly from mucous membranes, and that "Absorption has led to methemoglobinemia, exfoliative dermatitis and death in infants, * * *". The Panel recommended the warning "Do not use this product in children under 12 years of age except under the advice and supervision of a physician," (45 FR 35674). Further, a minority of the Panel concluded that the safety of 1 to 3 percent resorcinol for external use in OTC drug products remains to be established (45 FR 35666). This Panel also cited Cunningham (Ref. 3), who reviewed the literature and found seven cases of resorcinol poisoning from topical application in infants and young children. Six of the cited cases resulted in fatalities (Refs. 4 through 10). As discussed below, the cases frequently involved acute hemolytic anemia and methemoglobinemia.

Becker (Ref. 4) reported that a 42-day old infant suffering from extensive intertriginous eczema who was treated with one application of a 2 percent resorcinol/zinc paste reacted with vomiting, the passage of dark colored urine, and the development of an intense petechial skin eruption. In two days the infant's hemoglobin fell from 65 percent to 14 percent and the red blood cell count fell from 4,000,000 to 1,000,000 per cubic millimeter. The child died on the fifth day in spite of treatment with infusion of Ringer's solution and blood transfusion.

Nothen (Ref. 5) described poisoning in an 11-day-old infant suffering from pemphigus neonatorum who was found dead in bed some hours after the application of 3 percent resorcinol "vaseline."

Connerth (Ref. 6) reported on a 1½-year-old child with extensive eczema of the face and head who was first treated with a boric acid lotion and then for a few days with a 5-percent resorcinol zinc paste. The child became cyanosed and very ill. Hemoglobin fell to 45 percent, and there was associated hemoglobinemia and hemoglobinuria. The child died in convulsions.

Haenelt (Ref. 7) treated diaper rash in a 3-week-old infant with 5 percent resorcinol "vaseline." The infant was admitted to the hospital the next morning with severe cyanosis, burgundy colored urine, a hemoglobin of 53 percent, a red blood cell count of 2,900,000 per cubic millimeter, and bilirubin of 2.8 mg percent. The child deteriorated rapidly and died within 2 days. Death was due to methemoglobinemia.

Feigl (Ref. 8) described a 2-month-old infant suffering from generalized eczema who had been treated with resorcinol cream (concentration not stated). After 3 days, the child became desperately ill, developed convulsions, and died quickly.

Liebenam (Ref. 9) reported on a 36-day-old infant who had an intertriginous eczema diaper rash and was treated with a 20-percent resorcinol paste applied moderately thickly 5 to 6 times within 24 hours. The next day the child became gravely ill with intense general cyanosis. Hemoglobin fell to 65 percent and efforts to give blood intravenously were unsuccessful. The child died in convulsions 2 days after admission.

Kyrle (Ref. 10) reported on a 2-year-old boy with herpes tonsurans maculosus on the upper thighs treated with a 10-percent resorcinol lotion for 2

applications about 12 hours apart. After the second application, the boy's condition deteriorated rapidly. He became cyanosed with a weak irregular pulse and mild recurrent clonic fits. Within 12 hours, this condition improved but the boy developed a fever and severe dyspnea requiring oxygen therapy. He made a gradual recovery.

Cunningham (Ref. 3) discussed a case in which a 7-week-old infant was treated for diaper rash with an ointment containing 12.5 percent resorcinol. The ointment was applied on 4 occasions in less than a 24-hour period. After the fourth application, the mother noted that the infant shivered all over for about a minute. The infant's condition rapidly deteriorated during the day, and 6 hours later he was admitted to the hospital where the diagnosis of hemolytic anemia with hemoglobinuria was made. The infant developed a generalized papulo-squamous eruption which resulted in extensively desquamated skin over the body and a mass of thickened crusts on the scalp. Biochemical tests on the infant's blood serum and urine indicated that methemoglobin was also present. It was felt that the most likely cause was poisoning from a coal-tar derivative. Cunningham considered the diagnosis to be resorcinol poisoning. Urine tests for phenol derivatives were still positive 7 days after admission, but these phenol derivatives were not detected 13 days after admission. With blood transfusions and intravenous fluid, the infant made good progress and was discharged from the hospital after 27 days. However, it took more than 5 months for the infant's skin and scalp to fully heal.

Cunningham concluded that the above cases illustrate the danger of using resorcinol, even in the weakest lotion or ointment, topically on the skin of infants and young children. He stated that absorption may be intense and lethal where the skin is broken. He added that absorption may also occur and produce serious effects in sensitive subjects, even when the skin is almost intact. Cunningham concluded that resorcinol should not be used topically in the treatment of diaper rash, eczema, or other skin eruptions in childhood.

The agency notes that many of the infants in the above cases had diaper rash or eczema and that the concentration of resorcinol was similar to that found in marketed OTC diaper rash drug products. Based on the above incidences of poisoning resulting from the topical use of resorcinol on infants and children and the recommendations of several OTC drug advisory review panels, the agency considers resorcinol to be Category II for safety as an ingredient in diaper rash drug products.

References

(1) OTC Volume 160040.
(2) OTC Volume 020065.
(3) Cunningham, A. A., "Resorcin Poisoning," *Archives of Disease in Childhood*, 31:173–176, 1956.
(4) Becker, J., "Resorzin-Salbe verursacht todliche Vergiftung bei einem Saugling," *Sammlung von Vergiftungsfallen*, 4:7–8, 1933.
(5) Nothen, H., "Ueber Resorzinvergiftung bei auserer Anwendung," *Medizinische Klinik*, 4:901–902, 1908.
(6) Connerth, O., "Die Anwendung des Resorcins und seine Schadigungen im Kindesalter," *Zeitschrift Fur Kinderheilkunde*, 39:628–633, 1925.
(7) Haenelt, M., "Ein Fall von perkutaner Resorzinvergiftung," *Munchener Medizinische Wochenschrift*, 72:386, 1925.
(8) Feigl, J., "Neue Beobachtungen zur Kasuistik des Vorkommens von Hamatin im Menschlichen Blutserum. I," *Biochemische Zeitschrift*, 85:171–187, 1918.
(9) Liebenam, L., "Resorcin-Vergiftung im Sauglingsalter," *Sammlung von Vergiftungsfallen*, 6:175–176, 1935.
(10) Kyrle, J., "Beitrag zur Kenntnis der Resorzinvergiftung bei auserer Applikation des Mittels," *Dermatologische Zeitschrift*, 22:505–510, 1915.

M. Comment on Sodium Propionate

18. One manufacturer made submissions to the Antimicrobial I Panel (Ref. 1), the Antimicrobial II Panel (Ref. 2), and the Miscellaneous External Panel (Ref. 3) for two products labeled as containing sodium propionate and water-soluble derivatives of chlorophyll. One product containing 5 percent sodium propionate and 0.0125 percent water-soluble derivatives of chlorophyll was formulated in an emollient ointment base and labeled as having antiseptic and fungistatic action in the treatment of a number of skin conditions, including diaper rash. The other product contained 2.3 g sodium propionate and 6 mg water-soluble derivatives of chlorophyll in individual powder packets for use as a wet dressing. The product was labeled as being antiseptic and fungistatic to relieve inflammation and itching of skin irritations, fungus infections, and minor burns, but did not have diaper rash claims. The submissions included a number of studies and review articles in support of the safe and effective use of sodium propionate and water-soluble chlorophyllin in the treatment of a variety of dermatologic conditions (including diaper rash). In the submissions, it was stated that the concentration of the water-soluble chlorophyllin in these products was much lower than that used for treatment purposes in other products. According to the submissions, this ingredient was only included in these products to deodorize the propionate content and thereby make the preparation acceptable to patients.

Based on the manufacturer's statements about the concentration and role of water-soluble derivatives of chlorophyll (chlorophyllin) in these products, the agency considers this ingredient to be inactive in these products. This position is consistent with the recommendation of the Antimicrobial II Panel that also evaluated a submission for these products and determined that chlorophyll is an inactive or pharmaceutically necessary ingredient. (See the advance notice of proposed rulemaking for OTC topical antifungal drug products at 47 FR 12485.)

Sodium propionate has been evaluated by two panels and found safe for OTC use at concentrations up to 20 percent. The Vaginal Panel concluded that the propionates (calcium or sodium salts) are safe in concentrations of up to 20 percent for OTC use in vaginal drug products which claim to relieve minor irritations of the vagina (48 FR 46694 at 46704). Substantial clinical data (Ref. 4) had been submitted on a product containing 10 percent sodium propionate and 10 percent calcium propionate that had been marketed for 30 years for prescription use in women with mycotic vulvovaginitis. The agency notes that this Panel stated that it specifically considered fetal and infant systemic safety when vaginal drug products are used by pregnant or nursing women (48 FR 46699).

The Antimicrobial II Panel concluded that propionic acid and its salts (sodium propionate and zinc propionate) are safe for a total combined propionate concentration of 20 percent for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm (47 FR 12480 at 12547). This Panel noted that several submitted studies reported little local irritation from the topical use of propionates (Ref. 5). Some of these studies consisted of treatment regimens extending over several months with continuous use of propionates.

Propionic acid is one of several lower fatty acids occurring in sweat (Ref. 6). Peck and Russ (Ref. 7) explained, in their review of fatty acid therapy in general, that they were led to this treatment because their investigations had convinced them that human perspiration played a role as a protective mantle against skin infections. They further noted that, because fatty acids are more physiologic in their origin, they tend to be less

irritating and thus decrease the occurrence of local irritation and the development of dermatophytids which are often complicating sequela of the use of many antimicrobial chemicals. Sodium propionate was found to be less toxic in tissue culture tests than propionic acid (Ref. 8). Hara et al. (Ref. 9) reported that sodium and calcium propionates showed practically no toxicity when given to mice by oral administration in experiments of short duration. The propionates also showed no lowering of the growth curve when administered to rats by mouth in experiments of long duration, had no influence on hematological tests, and had no influence on both weights and volume of organs. No pathological changes upon histopathological examination and almost no detectable actions in general pharmacological tests were seen (Ref. 9).

Based on the above panel reviews and literature, it appears that there is no systemic toxicity hazard from topical absorption of sodium propionate. Nevertheless, the agency notes that very little data were submitted on topical use of this ingredient on infants. The agency concludes that before sodium propionate can be considered safe for OTC use in diaper rash drug products, studies should be conducted to determine the skin irritation and sensitization potential in infants when this ingredient is applied chronically under occlusion as occurs in the diaper area.

The agency is also concerned about the effect of sodium propionate on the skin flora under the occlusive conditions found in the diaper area when this ingredient is used chronically on infants and children. The agency believes that further in vivo bacteriological studies are needed, specifically in infants, to demonstrate the effect of the antibacterial activity of sodium propionate on the skin flora and whether this correlates with clinical improvements in diaper rash, and further whether long-term use of sodium propionate results in potentially harmful changes in the normal flora of the skin in the diaper area.

The manufacturer's submissions contained several articles (Refs. 10, 11, and 12) that discussed the use of products containing sodium proprionate as a therapeutic agent. Peck, Traub, and Spoor (Ref. 12) reported that in a small series of cases the combination of chlorophyllin-sodium propionate as a wet dressing and the use of an ointment containing 5 percent sodium propionate and 0.0125 percent chlorophyllin seemed to be an effective treatment for diaper rash. The wet dressing quickly controlled the acute symptoms, while the ointment acted as a healing and protective application and helped prevent recurrences. Edelson (Ref. 13) reported on use of the product in six patients with severely excoriated and macerated diaper eruptions: three made very prompt improvement using the wet dressing solution after each diaper change and as a regular cleansing agent with cotton; one patient improved moderately well, but after 1 week needed more active therapy; one infant showed no change in 4 days; and one infant cried bitterly with any watery application but did well with a paste application containing other ingredients. Noojin, Osment, and Taylor (Ref. 14) mention use of the product on 11 patients with infantile eczema, but no information is provided as to whether the condition was diaper rash. Other authors (Refs. 13 and 14) have shown that in in vitro studies sodium propionate inhibits the growth of bacteria including *S. aureus*, beta hemalytic streptococcus, *E. coli*, and *P. aeruginosa*.

The agency finds the submitted information inadequate to establish the safety and effectiveness of sodium propionate for antiseptic or antifungal use in diaper rash drug products. The number of infants with diaper rash who were studied was very limited. None of the information is from a well-controlled clinical study. Further, the Antimicrobial II Panel found the data it reviewed insufficient to establish the effectiveness of propionic acid and its salts (sodium propionate and zinc propionate) as an antifungal in the treatment of athlete's foot, jock itch, and ringworm. That Panel stated that "In vitro antifungal data suggest that propionates are bacteriostatic and fungistatic," but that the "* * * data is quite old and uses zone of inhibition and contact-time testing so that only general conclusions can be drawn." (See 47 FR 12547.) No additional data were submitted in response to the advance notice of proposed rulemaking. Propionates remain classified in Category III in the tentative final monograph for OTC antifungal drug products (54 FR 51136 at 51156).

The agency concludes that the available data are inadequate to support the antimicrobial or antifungal use of sodium propionate in diaper rash drug products and classifies the ingredient as Category III for both safety and effectiveness.

References

(1) OTC Volume 020146.
(2) OTC Volume 070146.
(3) OTC Volume 160105.
(4) OTC Volumes 110027 and 070031.
(5) OTC Volume 070032.
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(11) Edelson, E., "A New Wet Dressing in Dermatology," *Medical Times*, 82:37-43, 1954.
(12) Noojin, R.O., L.S. Osment, and C.D. Taylor, "The Local Use of Wet Dressings Utilizing Sodium Propionate Plus Chlorophyll," *American Practitioner and Digest of Treatment*, 5:186-188, 1954.
(13) Theodore, F.H., "Use of Sodium Propionate in External Infections of the Eyes," *Journal of the American Medical Association*, 143:226–228, 1950.
(14) Keeney, E.L., et al., "Propionate and Undecylenate Ointments in the Treatment of Tinea Pedis and an In Vitro Comparison of their Fungistatic and Antibacterial Effects with Other Ointments," *Bulletin Johns Hopkins Hospital*, 75:417–439, 1944.

N. Comment on Triclosan

19. Several submissions to the Antimicrobial I Panel and comments to the rulemaking for OTC topical antimicrobial drug products were made by the manufacturer of a medicated powder product containing triclosan (0.1 percent), corn starch, zinc oxide, and kaolin as active ingredients (Refs. 1 and 2). The product was labeled for use in a number of skin conditions, including diaper rash and chafing. It was also labeled as "helps prevent urine irritation" and "kills millions of diaper rash germs." The submissions included animal and human safety data pertaining to triclosan, reports of in vitro antimicrobial efficacy of triclosan, and a report of in vitro antimicrobial efficacy of the finished product. The manufacturer contended that the product has excellent activity against urea-splitting organisms which are contributing factors in diaper rash. The

manufacturer of triclosan also submitted safety and efficacy data (Ref. 3) that included reports of antibacterial activity and ammonia inhibition of diapers rinsed with a fabric softener containing triclosan. However, no labeling for any commercial product for diaper rinse use was provided.

The Antimicrobial I Panel (39 FR 33102 at 33127) reviewed triclosan for use in topically applied antimicrobial products and classified it in Category III for both safety and effectiveness. The Panel expressed concerns about its chronic use and about its use on infants under 6 months of age. The Panel noted that glucuronide conjugation is "a major route of elimination of triclosan from the body" and that "this mechanism may be deficient in young animals and human infants." The Panel also pointed out the need for safety data relevant to long-term use and recommended a label warning "Do not use this product on infants under 6 months of age," for products containing triclosan.

Subsequent to the publication of the Panel's report, the manufacturer of triclosan submitted validation reports and raw data from a 2-year chronic oral toxicity study in rats by Industrial Bio-Test Laboratories (IBT) (Ref. 4). With regard to safety, the agency evaluated the validation reports to support long-term use of the ingredient and advised the manufacturer of triclosan that the 2-year chronic oral toxicity studies were invalid because of numerous problems. The agency's detailed comments and evaluations on the data are on file in the Dockets Management Branch (Ref. 5).

The manufacturer subsequently stated its intent to no longer rely on the earlier 2-year chronic oral toxicity IBT study (Ref. 6). Recently, the manufacturer submitted a final report from a new 2-year chronic oral toxicity study in rats which the agency is evaluating (Ref. 7).

The same manufacturer also submitted safety data pertaining to neonate rhesus monkeys bathed in soap containing 0.1 percent triclosan (Ref. 8). The agency has evaluated the data and determined that the bathing study in neonate rhesus monkeys contributes little to support the safe use of triclosan for human infants because of the low exposure dose of 0.1 percent triclosan. Although the study demonstrated that neonate monkeys, like human neonates, can metabolize triclosan in more than one way and would not be disposed to liver damage, even at the low exposure level, tissue levels approached 2 parts per million. A study using a greater area of application, more frequent bathing, and a higher concentration of triclosan would be more supportive to establish safe use in diaper rash drug products.

Another study on absorption, metabolism, and excretion in newborn and adult rhesus monkeys indicated that both handle triclosan similarly, the sulfate ester predominating. Sulfate conjugation is better developed in infants than glucuronide conjugation. However, this does not imply that there is no problem. An infant has the same problem as an adult—persistence due to the sulfate ester. The agency is also concerned about the use of a phenolic compound in infants and cannot make a final risk assessment without adequate data. The agency considers the benefit-to-risk ratio to be unacceptably small if there is any potential risk at all.

Pending completion of the agency's evaluation of the new 2-year study (Ref. 7) and the submission of additional data, as discussed above, triclosan remains classified in Category III for safety for long-term use in infants. Further, the agency is aware that the Environmental Protection Agency (EPA) denied a request by the manufacturer of triclosan to remove the label warning on fabric softeners containing triclosan that states "Do not use for baby diaper laundry," (Ref. 9). This remains EPA's current position (Ref. 10).

Jungermann and Taber (Ref. 11) briefly discussed a study on 151 infants to test for mildness of two bath soaps: (1) A test soap containing 0.1 percent triclosan, 1 percent hexachlorophene, and 1 percent triclocarban; and (2) a nonmedicated soap (Ivory). The protocol was an 8-week blind cross-over where one group of infants is bathed exclusively with one of the soaps for 4 weeks and then with the other soap for another 4 weeks. The condition of the skin in general and of the diaper area in particular was examined each week. Nurses bathing the infants used the same soap for their own washing. Apparently only 51 infants remained in the hospital long enough to complete the trial of 4 weeks with each soap. The other infants were bathed with each soap for varying (unspecified) shorter periods. The authors stated that there was no evidence of primary irritation or allergic contact dermatitis from use of either soap but did not give any further details.

The agency notes that very little data were submitted on the topical use of triclosan on infants, particularly for diaper rash. The agency has determined that studies should be conducted to determine the skin irritation and sensitization potential in infants when this ingredient is applied chronically under occlusion as occurs in the diaper area.

The submissions from manufacturers of the ingredient and the product include in vitro tests of the antimicrobial effectiveness of triclosan. These tests include studies on the inhibition of ammonia production in diapers rinsed with a fabric softener containing triclosan. The results indicate that triclosan is bacteriostatic against a wide range of gram negative and gram positive species, as well as many fungi.

The agency has evaluated the role of bacteria in causing or aggravating diaper rash (see comments 1 and 2 above) and has concluded that more data are needed regarding the intended effect of antimicrobial treatment of diaper rash. The agency has concerns about the safety and efficacy of continuously and routinely using antimicrobial drugs in the diaper area just for the purpose of generally reducing the microflora count. The agency believes that further in vivo bacteriological studies are needed, specifically in infants. These studies need to demonstrate the effect of the antibacterial activity of triclosan on the skin flora and show whether this correlates with clinical improvements in diaper rash. They also need to determine whether long-term use of triclosan results in potentially harmful changes in the normal flora of the skin in the diaper area.

The data submitted for triclosan do not adequately address these concerns. Most of the studies were performed in vitro or involved the use by adults of triclosan formulated in antimicrobial soap. The one report of triclosan-containing soap used in infants pertained to the evaluation of the mildness of the soap to infant skin (Ref. 11) and did not address the issue of bacterial involvement in diaper dermatitis or demonstrate clinical effectiveness. More information, as discussed above, is needed before triclosan can be placed in Category I for the prevention or treatment of diaper rash. Accordingly, the agency is classifying triclosan for use in diaper rash drug products in Category III for both safety and effectiveness.

References

(1) OTC Volumes 020077, 020078, and 020079.

(2) Comment Nos. C00114 and SUP020, Docket No. 75N-0183, Dockets Management Branch.

(3) OTC Volumes 020033, 020034, 020035, 020036, 020037, 020038, 020039, and 020040.

(4) "Two-Year Chronic Oral Toxicity Study With FAT 80' 023/A in Albino Rats," Comment No. C00109, Volume 1, Appendix E, and Comment No. C00139, Volumes 1 through 8, Docket No. 75N-0183, Dockets Management Branch.

(5) Letter from W.E. Gilbertson, FDA, to R. Bernegger, Ciba-Geigy Corp., coded LET028/

ANS, Docket No. 75N–0183, Dockets Management Branch.

(6) Memorandum of Meeting between FDA Staff and Representatives of Ciba-Geigy Corp., September 6, 1983, Comment No. MM0007, Docket No. 75N–0183, Dockets Management Branch.

(7) "FAT 80' 023 2-Year Oral Administration in Rats," Volumes XLI, XLII, and XLIII and "Determination of FAT 80' 023 in Blood and Tissue Samples Taken During a Two-Year Chronic Oral Toxicity/Oncogenicity Study in Albino Rats," Volume XLIV, Comment No. RPT002, Docket No. 75N–0183, Dockets Management Branch.

(8) Comment No. C00109, Docket No. 75N–0183, Dockets Management Branch.

(9) Letter from A.E. Castillo, EPA, to J. LoMenzo, Ciba-Geigy Corp., dated September 21, 1982, in OTC Volume 02DTFM, Docket No. 75N–183D, Dockets Management Branch.

(10) Memorandum of telephone conversation between W. Campbell, EPA, and L. Geismar, FDA, dated January 6, 1988, in OTC Volume 02DTFM, Docket No. 75N–183D, Dockets Management Branch.

(11) Jungermann, E., and D. Taber, "A New Broad Spectrum Antibacterial Soap: 1. General Properties," *Journal of the American Oil Chemists' Society*, 48:318–323, 1971.

O. Comment on Testing

20. One comment submitted a number of recommendations for criteria for evaluating diaper rash ingredients and included protocols for two clinical studies to demonstrate both treatment and prevention of diaper rash. Although the comment directed most of its statements to skin protectant drug products, it also recommended that diaper rash combination products containing skin protectant and nonskin protectant active ingredients meet the criteria for skin protectants as well as the criteria established under the appropriate monographs for the other ingredients, e.g., antimicrobials, antifungals, or external analgesics.

This comment is discussed in detail in comment 34 of the tentative final monograph for OTC skin protectant diaper rash drug products, published elsewhere in this issue of the Federal Register. The agency states in that comment that testing guidelines for skin protectant diaper rash ingredients would not be included in that document and any interested person wanting advice on Category III testing should communicate directly with the agency. Similarly, testing guidelines for antimicrobial diaper rash ingredients are not being included in this document. (See also part III. paragraph A.2. below—*Testing of Category II and Category III conditions.*)

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 topical antimicrobial drug products: alkyldimethyl benzylammonium chloride,[1] benzethonium chloride, chloroxylenol, hexachlorophene, methylbenzethonium chloride, p-chloromercuriphenol, phenol and phenylmercuric nitrate. The agency has reviewed the submissions to the Miscellaneous External Panel and determined that 21 submissions (Ref. 1) relate to products containing these ingredients for use in the treatment of diaper rash.

A number of submissions (Ref. 2) to the Antimicrobial I and II Panels included products containing antimicrobial ingredients (benzalkonium chloride, boric acid, calcium undecylenate, chloroxylenol, hexachlorophene, methylbenzethonium chloride, p-chloromercuriphenol, resorcinol, sodium propionate (with chlorophyll derivatives) and triclosan) labeled for use in the treatment and prevention of diaper rash. Some of these ingredients (sodium propionate (with chlorophyll derivatives) and triclosan) were not included in the Miscellaneous External Panel's statement. In addition, a number of comments (Ref. 3) received in response to the tentative final monograph for OTC topical antimicrobial drug products (January 6, 1978; 43 FR 1210) were relevant to the use of these antimicrobial ingredients in diaper rash. The agency has also included these submissions and comments in this rulemaking.

References

(1) OTC Volumes 160025, 160027, 160040, 160042, 160059, 160060, 160077, 160091, 160105, 160221, 160235, 160236, 160242, 160243, 160244, 160245, 160246, 160247, 160320, 160357, and 160427.

(2) OTC Volumes 020001, 020008, 020016, 020023, 020026, 020028, 020030, 020033, 020034, 020035, 020036, 020037, 020038, 020039, 020040, 020044, 020046, 020051, 020065, 020077, 020078, 020079, 020088, 020146, 020188, 070007, 070021, 070029, 070031, 070032, 070074, 070075, 070076, 070077, 070078, 070079, and 070146.

(3) Comments No. RPT005, RPT00006, C00048, C00061, C00109, C00114, C00116, C00163, SUP013, SUP018, SUP020, SUP028, Docket No. 75N–0183, Dockets Management Branch.

[1] The agency has determined that the name "benzalkonium chloride" is the preferred name for this ingredient.

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 antimicrobial ingredients for the treatment of diaper rash, it did not classify any 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 39406). The Panel recommended that several of the antimicrobial ingredients included in this list be referred to the rulemaking for OTC topical antimicrobial drug products and recommended that the other ingredients be referred to the rulemaking(s) that FDA considered most appropriate. In publishing the Panel's statement, the agency requested public comment from interested persons.

The agency has reviewed all claimed active ingredients submitted to the Miscellaneous External Panel, the recommendations of the Antimicrobial I Panel (39 FR 33102), the tentative final monograph on OTC topical antimicrobial drug products (43 FR 1210), and other data and information available at this time. Based upon this information, the agency is proposing the following categorization of antimicrobial active ingredients for the treatment and prevention of diaper rash:

Ingredient	Category
Benzalkonium chloride	III
Benzethonium chloride	III
Boric acid	II
Calcium undecylenate	III
Chloroxylenol	III
Hexachlorophene	II
Methylbenzethonium chloride	III
Oxyquinoline	III
P-Chloromercuriphenol	II
Phenol	II
Resorcinol	II
Sodium propionate	III
Triclosan	III

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 antimicrobial 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. The agency has proposed labeling in this tentative final monograph in the event that new data are submitted to establish "monograph conditions" for OTC topical antimicrobial active ingredients for the treatment or prevention of diaper rash. This labeling is similar to that proposed for OTC skin protectant diaper rash drug products, elsewhere in this issue of the Federal Register, with some minor modifications to reflect the topical antimicrobial action of these products.

In the event that no new data are submitted to the agency during the alloted 12-month new data period or if the submitted data are not sufficient to establish "monograph conditions" for OTC topical antimicrobial drug products for the treatment or prevention of diaper rash, the agency will consider such products to be new drugs under section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321), for which applications approved under section 505 of the act (21 U.S.C. 355) and 21 CFR part 314 are required for marketing. If this occurs, upon the effective date of that portion of the final rule for OTC topical antimicrobial drug products that applies to OTC diaper rash drug products, any OTC drug products containing topical antimicrobial 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 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 topical antimicrobial 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 topical antimicrobial 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 topical antimicrobial 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 topical antimicrobial 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 topical antimicrobial 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 topical antimicrobial 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 topical antimicrobial 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 topical antimicrobial 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 333

Diaper rash drug products, Labeling, Over-the-counter drugs.

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 333 as follows:

PART 333—TOPICAL ANTIMICROBIAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. In part 333 by adding a new subpart F as follows:

Subpart F—Diaper Rash Drug Products

Sec.

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).

Subpart F—Diaper Rash Drug Products

§ 333.501 Scope.

(a) An over-the-counter diaper rash drug product in a form suitable for topical administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this subpart and each of the general conditions established in § 330.1 of this chapter.

(b) References in this subpart to regulatory sections of the Code of Federal Regulations are to chapter I of title 21 unless otherwise noted.

§ 333.503 Definitions.

As used in this subpart:

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.

§ 333.510 Diaper rash active ingredients. [Reserved]

§ 333.550 Labeling of diaper rash drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "antiseptic diaper rash" (insert dosage form, e.g., "ointment," "cream," or "powder").

(b) *Indications.* The labeling of the product states under the heading "Indications," the following: "Helps" (select one or more of the following: "reduce," "guard against," or "protect against") (select one of the following: "infection" or "skin infection") "associated with diaper rash." 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 Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of 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.

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

(1) "For external use only."

(2) "Avoid contact with the eyes."

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

(4) *For powder products only.* "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 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."

(2) *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."

Dated: April 24, 1990.

James S. Benson,

Acting Commissioner of Food and Drugs.

[FR Doc. 90-13851 Filed 6-19-90; 8:45 am]

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federal register

Wednesday
June 20, 1990

Part VI

Department of Labor

Pension and Welfare Benefits Administration

29 CFR Parts 2560 and 2570

Interim and Proposed Regulations Relating to Civil Penalties Under ERISA Section 502(l)

DEPARTMENT OF LABOR

Pension and Welfare Benefits Administration

29 CFR Part 2570

RIN 1210-AA37

Interim Regulation Relating to Civil Penalties Under ERISA Section 502(l)

AGENCY: Pension and Welfare Benefits Administration, Department of Labor.

ACTION: Interim rule.

SUMMARY: This document contains an interim regulation that describes the procedures relating to the assessment of civil penalties under section 502(l) of the Employee Retirement Income Security Act of 1974, as amended (ERISA or the Act). A separate document which contains a proposed regulation defining certain terms under ERISA section 502(l) is also being published today.

Section 502(l) requires the Secretary of Labor (the Secretary) to assess a civil penalty against a fiduciary who breaches a fiduciary responsibility under, or commits any other violation of, part 4 of title I of ERISA or any other person who knowingly participates in such breach or violation. The regulation sets forth the procedures for the assessment of penalties under ERISA section502(l) and for petitioning the Secretary to exercise his or her discretion to waive or reduce the mandated assessment.

DATES: This interim regulation is effective June 20, 1990, and will apply to any assessment made by the Secretary after June 20, 1990 based on any breach of fiduciary responsibility under, or other violation of, part 4 of title I of ERISA occurring on or after December 19, 1989. Written comments concerning this interim rule must be received by the Department of Labor (the Department) on or before August 20, 1990.

ADDRESSES: Interested persons are invited to submit written comments concerning this interim rule to: Pension and Welfare Benefits Administration, room N-5671, U.S. Department of Labor, 200 Constitution Ave., NW, Washington, DC 20210. Attention: Interim section 502(l) Civil Penalty Rule. All submissions will be open to public inspection at the Public Documents Room, Pension and Welfare Benefits Administration, U.S. Department of Labor, room N-5507, 200 Constitution Ave., NW., Washington, DC 20210.

FOR FURTHER INFORMATION CONTACT: Vicki Shteir-Dunn, Plan Benefits Security Division, Office of the Solicitor, (202) 523-9596, and David Lurie, Office of Regulations and Interpretations, Pension and Welfare Benefits Administration, (202) 523-8671.

SUPPLEMENTARY INFORMATION: Section 502(l) requires the Secretary to assess a civil penalty against a fiduciary who breaches a fiduciary responsibility under, or commits a violation of, part 4 of title I of ERISA or any other person who knowingly participates in such breach or violation.[1] The penalty under section 502(l) is equal to 20 percent of the "applicable recovery amount" paid pursuant to any settlement agreement with the Secretary or ordered by a court to be paid in a judicial proceeding instituted by the Secretary under section 502(a)(2) or (a)(5). The Secretary may, in the Secretary's sole discretion, waive or reduce the penalty if the Secretary determines in writing that either: (1) The fiduciary or other person acted reasonably and in good faith, or (2) it is reasonable to expect that the fiduciary or other person will not be able to restore all losses to the plan or any participant or beneficiary of such plan without severe financial hardship unless such waiver or reduction is granted. The penalty imposed on a fiduciary or other person with respect to any transaction shall be reduced by the amount of any penalty or tax imposed on such fiduciary or other person with respect to such transaction under ERISA section 502(i) or section 4975 of the Internal Revenue Code of 1986 (the Code). A separate notice of proposed rulemaking dealing with the definition of the terms "applicable recovery amount", "breach of fiduciary responsibility", "violation", "continuing violation", "settlement agreement", and "court order" is also being published today.

In general, the interim regulation addresses the procedures under which a penalty will be assessed (§ 2570.83), when an assessed penalty must be paid (§ 2570.84, and the circumstances pursuant to which the Secretary may waive or reduce a penalty (§§ 2570.85 and 2570.86). Specifically, subsequent to the payment of the applicable recovery amount pursuant to either a settlement agreement or a court order, the Secretary [2] will serve on the person liable for making such payment a notice of assessment of civil penalty equal to 20 percent of the applicable recovery amount. The "notice of assessment" is defined generally as any document, however designated, issued by the Secretary which contains a specified assessment, in monetary terms of a civil penalty under ERISA section 502(l). A "notice of assessment" will also contain a brief factual description of the violation for which the assessment is being made, the identity of the person being assessed, and the amount of the assessment and the basis for assessing that particular person that particular penalty amount.

Service of the notice of assessment will be made in one of three ways: (1) By delivering a copy to the person being assessed; if the person is a partnership, any partner; if the person is a corporation, association, exchange, or other entity or organization, any officer of such entity; if the person is an employee benefit plan, a trustee of such plan; or any attorney representing the person in this matter; (2) by leaving a copy at the principal office, place of business, or residence of such individual, partner, officer, trustee, or attorney; or (3) by mailing a copy to the last known address of such individual, partner, officer, trustee, or attorney. If service is accomplished by certified mail, service is complete upon mailing. If done by regular mail, service is complete upon receipt by the addressee.

A person being assessed a penalty will have 60 days from the service of the notice of assessment to pay the assessed amount. Subject to any tolling of this 60-day payment period during the consideration of a waiver or reduction petition described below, the notice of assessment will become a final agency action (within the meaning of 5 U.S.C. 704) on the first day following the 60-day period. At any time prior to the expiration of that 60-day period, a person may request a conference with the Secretary to discuss the calculation of the assessment or may petition the Secretary to waive or reduce the assessed penalty. In the case of a request to discuss the calculation of the assessment, the Secretary will schedule such conference as soon as is administratively feasible. The 60-day payment period will not, however, be tolled upon such request.[3]

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[1] Section 502(l) was added to ERISA by section 2101 of the Omnibus Budget Reconciliation Act of 1989.

[2] In this regard, the Secretary has established the Pension and Welfare Benefits Administration within the Department for the purpose of carrying out most of the Secretary's responsibilities under ERISA. See, Secretary's Order 1-87, 52 FR 13139 (April 21, 1987). Thus, the Department contemplates that the duties assigned to the Secretary under this procedural regulation will in fact be discharged by the Assistant Secretary for Pension and Welfare Benefits or the appropriate Area Director or Deputy Area Director.

[3] If, based on a conference, the Secretary determines that a factual mistake has occurred which reduces the amount of the penalty already paid, a refund of that mistaken overpayment will be made as soon as is administratively feasible. See § 2570.87 concerning the revision of assessments.

At any time prior to the expiration of the 60-day payment period, a person may also petition the Secretary to waive or reduce the assessed penalty on one of two grounds: (1) That the person acted reasonably and in good faith in engaging in the breach or violation; [4] or (2) the person will not be able to restore all losses to the plan or any participant or beneficiary of such plan without severe financial hardship unless such waiver or reduction is granted.[5] A petition to waive or reduce must be in writing and contain the following information: (1) The name of the petitioner; (2) a detailed description of the breach or violation which is the subject of the penalty; (3) a detailed recitation of the facts which support one, or both, of the bases for waiver or reduction described above, accompanied by underlying documentation supporting such factual allegations; and (4) a declaration, signed and dated by the petitioner, which states that under penalty of perjury, the petitioner is making true and correct representations to the best of his or her knowledge and belief.

If the petition for waiver or reduction of penalty is submitted during the 60 day payment period, the payment period for the penalty in question will be tolled pending Departmental consideration of the petition. During such consideration, the petitioner is also entitled to one conference with the Secretary. The Secretary may, however, in his or her sole discretion, schedule or hold additional conferences with the petitioner concerning the factual allegations contained in the petition. Once the Secretary has made a determination with regard to the petition, the petitioner will be served a written determination briefly informing him of the Secretary's decision and the grounds for that decision. Such determination is solely within the Secretary's discretion and is a final, non-reviewable order. In those situations where the Secretary concludes that no waiver or reduction shall be granted, the payment period for the penalty in question, if previously initiated, will resume as of the date of service of the determination on the petitioner.[6]

Any penalty assessed under ERISA section 502(l) and this rule on a person with regard to any particular transaction will be reduced by the amount of any penalty or tax imposed on such person with respect to such transaction under ERISA section 502(i) and section 4975 of the Code. Prior to such a reduction, the person being assessed must provide proof to the Department of his or her payment of the penalty or tax and the amount of such payment. Submissions of proof of other penalty or tax assessments will not toll the 60-day payment period, if previously initiated.

If, based on information gained through a conference, waiver or reduction petition, or submission of proof of other penalty or tax payment, the Department determines that a previously issued notice of assessment should be revised, the Department shall issue a revised notice of assessment to the person being assessed, and that person will be obligated to pay the revised assessed penalty within the relevant 60-day period (as determined by the applicable procedure in §§ 2570.84, 2570.85, or 2570.86), and, where necessary, any excess penalty payment will be refunded as soon as administratively feasible. The revised notice of assessment will revoke any previously issued notice with regard to the transaction in question, and will become a final order (within the meaning of 5 U.S.C. 704) the later of the first day following the 60-day payment period or the date of its service on the person being assessed, pursuant to the service procedures described in § 2570.83(b).

Because this rule deals solely with agency procedures and is not a substantive rule, the Administrative Procedure Act (APA) at 5 U.S.C. 553(b)(3)(A) permits its publication without notice or opportunity for comment, and 5 U.S.C. 553(d) permits this rule to become effective immediately. Moreover, due to the statutory mandate requiring the Secretary to assess penalties under ERISA section 502(l) based on any breach or violation occurring on or after December 19, 1989, as well as the need to continue unabated the Department's ERISA enforcement efforts (e.g., settlement agreements through voluntary compliance), the Department is promulgating this rule effective immediately. As promulgated, the rule will apply to assessments made by the Secretary after June 20, 1990, based on any breaches or violations occurring on or after December 19, 1989. Published today is a separate notice of proposed rulemaking defining, among other terms, what constitutes a violation for purposes of ERISA section 502(l).

Regulatory Flexibility Act Statement

The Regulatory Flexibility Act imposes certain requirements with respect to rules which would have a significant impact on a substantial number of small entities. A "rule" under the Regulatory Flexibility Act is one for which a general notice of proposed rulemaking is required under section 553(b) of the Administrative Procedure Act. Under section 553(b) of the Administrative Procedure Act, a general notice of proposed rulemaking is not required for rules of agency organization, procedure or practice. Thus, such rules are excluded from the definition of "rule" under the Regulatory Flexibility Act. Since this procedural regulation is a rule of agency procedure or practice, it is not subject to the requirements of the Regulatory Flexibility Act.

Executive Order 12291

The Department has determined that this regulatory action would not constitute a "major rule" as that term is used in Executive Order 12291 because the action does not result in: An annual effect on the economy of $100 million; a major increase in costs or prices for consumers, individual industries, government agencies, or geographic regions; or significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of United States-based enterprises to compete with foreign-based enterprises in domestic or export markets.

Paperwork Reduction Act

The Paperwork Reduction Act mandates that agencies provide data with respect to information collection requirements which may be imposed by certain regulatory actions. Section 3518(c)(1)(B) of the Paperwork Reduction Act provides that the requirements of the Act do not apply to

[4] As a general matter, in determining whether a fiduciary or knowing participant acted reasonably and in good faith, the Department will examine the decisionmaking process with respect to the transaction in question to determine whether it was designed to adequately safeguard the interests of the participants and beneficiaries of the plan. In absence of such a decisionmaking process, actual favorable investment return to the plan will not provide a sufficient showing that a person acted reasonably and in good faith with regard to a particular transaction. See ERISA Technical Release Number 85–1 for general guidelines concerning the Department's previously-articulated views concerning evidence of good faith.

[5] A person may make these arguments not only with regard to actual losses to the plan, but also with regard to any disgorgement of profits gained through the relevant breach or violation or amounts necessary for transfer to the plan in order to correct the relevant breach or violation.

[6] Service of the petition determination will be achieved in a similar fashion to that of the notice of assessment. Thus, in calculating the resumption of the 60-day payment period, refer to the previous discussion concerning service of the notice of assessment for purposes of determining when service is achieved. See also paragraph 2570.87 concerning the procedure for the revision of previously issued notices of assessments.

administrative actions involving specific individuals or entities. The Department has determined that the administrative adjudications which would be conducted pursuant to the procedures contained in this regulation fall within the scope of this exemption from the Paperwork Reduction Act.

Statutory Authority

This Interim Rule is adopted pursuant to the authority contained in section 505 of ERISA (Pub. L. 93–406, 88 Stat. 892, 894; 29 U.S.C. 1135).

List of Subjects in 29 CFR Part 2570

Administrative practice and procedure, Employee benefit plans, Employee Retirement Income Security Act, Party in interest, Law enforcement, Pensions, Pension and Welfare Benefits Administration, Prohibited transactions.

Interim Rule

In view of the foregoing the Department is amending part 2570 of chapter XXV of title 29 of the Code of Federal Regulations as follows:

PART 2570—[AMENDED]

By adding in the appropriate place in part 2570 the following new subpart D:

Subpart D—Procedure for the Assessment of Civil Penalties Under ERISA Section 502(1)

Sec.

Subpart D—Procedure for the Assessment of Civil Penalties Under ERISA Section 502(l)

§ 2570.80 Scope of rules.

The rules of practice set forth in this subpart are applicable to "502(l) civil penalty proceedings" (as defined in § 2570.82 of this subpart) under section 502(l) of the Employee Retirement Income Security Act of 1974 (ERISA or the Act). Refer to 29 CFR 2560.5021 for the definition of the relevant terms of ERISA section 502(l).

§ 2570.81 In general.

Section 502(l) of the Employee Retirement Income Security Act of 1974 (ERISA or the Act) requires the Secretary of Labor to assess a civil penalty against a fiduciary who breaches a fiduciary responsibility under, or commits any other violation of, part 4 of Title I of ERISA or any other person who knowingly participates in such breach or violation. The penalty under section 502(l) is equal to 20 percent of the "applicable recovery amount" paid pursuant to any settlement agreement with the Secretary or ordered by a court to be paid in a judicial proceeding instituted by the Secretary under section 502 (a)(2) or (a)(5). The Secretary may, in the Secretary's sole discretion, waive or reduce the penalty if the Secretary determines in writing that:

(a) The fiduciary or other person acted reasonably and in good faith, or

(b) It is reasonable to expect that the fiduciary or other person will not be able to restore all losses to the plan or any participant or beneficiary of such plan without severe financial hardship unless such waiver or reduction is granted.

The penalty imposed on a fiduciary or other person with respect to any transaction shall be reduced by the amount of any penalty or tax imposed on such fiduciary or other person with respect to such transaction under section 502(i) or section 4975 of the Internal Revenue Code of 1986 (the Code).

§ 2570.82 Definitions.

For purposes of this section:

(a) *502(l) civil penalty proceedings* means an adjudicatory proceeding relating to the assessment of a civil penalty provided in section 502(l) of ERISA;

(b) *Notice of assessment* means any document, however designated, issued by the Secretary which contains a specified assessment, in monetary terms, of a civil penalty under ERISA section 502(l). A "notice of assessment" will contain a brief factual description of the violation for which the assessment is being made, the identity of the person being assessed, and the amount of the assessment and the basis for assessing that particular person that particular penalty amount;

(c) *Person* includes an individual, partnership, corporation, employee benefit plan, association, exchange or other entity or organization;

(d) *Petition* means a written request, made by a person, for a waiver or reduction of the civil penalty described herein; and

(e) *Secretary* means the Secretary of Labor and includes, pursuant to any delegation of authority by the Secretary, the Assistant Secretary for Pension and Welfare Benefits, Area Directors for Pension and Welfare Benefits, or Deputy Area Directors for Pension and Welfare Benefits.

§ 2570.83 Assessment of civil penalty.

(a) Except as described in §§ 2570.85 and 2570.86 below, subsequent to the payment of the applicable recovery amount pursuant to either a settlement agreement or a court order, the Secretary shall serve on the person liable for making such payment a notice of assessment of civil penalty equal to 20 percent of the applicable recovery amount.

(b) Service of such notice shall be made either:

(1) By delivering a copy to the person being assessed; if the person is an individual, to the individual; if the person is a partnership, to any partner; if the person is a corporation, association, exchange, or other entity or organization, to any officer of such entity; if the person is an employee benefit plan, to a trustee of such plan; or to any attorney representing any such person;

(2) By leaving a copy at the principal office, place of business, or residence of such individual, partner, officer, trustee, or attorney; or

(3) By mailing a copy to the last known address of such individual, partner, officer, trustee, or attorney.

If service is accomplished by certified mail, service is complete upon mailing. If done by regular mail, service is complete upon receipt by the addressee.

§ 2570.84 Payment of civil penalty.

(a) The civil penalty must be paid within 60 days of service of the notice of assessment.

(b) At any time prior to the expiration of the payment period for the assessed penalty, any person who has committed, or knowingly participated in, a breach or violation, or has been alleged by the Secretary to have so committed or participated, may submit a written request for a conference with the Secretary to discuss the calculation of the assessed penalty. A person will be entitled under this section to one such conference per assessment. If such written request is submitted during the 60 day payment period described in subparagraph (a), such a request will not toll the running of that payment period.

(c) The notice of assessment will become a final order (within the meaning of 5 U.S.C. 704) on the first day following the 60 day payment period, subject to any tolling caused by a petition to waive or reduce described in paragraph 2570.85.

§ 2570.85 Waiver or reduction of civil penalty.

(a) At any time prior to the expiration of the payment period for the assessed penalty, any person who has committed, or knowingly participated in, a breach or violation, or has been alleged by the Secretary to have so committed or participated, may petition the Secretary to waive or reduce the penalty under this section on the basis that:

(1) The person acted reasonably and in good faith in engaging in the breach or violation; or

(2) The person will not be able to restore all losses to the plan or participant or beneficiary of such plan without severe financial hardship unless such waiver or reduction is granted.

(b) All petitions for waiver or reduction shall be in writing and contain the following information:

(1) The name of the petitioner(s);

(2) A detailed description of the breach or violation which is the subject of the penalty;

(3) A detailed recitation of the facts which support one, or both, of the bases for waiver or reduction described in § 2570.85(a) of this part, accompanied by underlying documentation supporting such factual allegations;

(4) A declaration, signed and dated by the petitioner(s), in the following form: Under penalty of perjury, I declare that, to the best of my knowledge and belief, the representations made in this petition are true and correct.

(c) If a petition for waiver or reduction is submitted during the 60 day payment period described in § 2570.84(a) above, the payment period for the penalty in question will be tolled pending Departmental consideration of the petition. During such consideration, the applicant is entitled to one conference with the Secretary, but the Secretary, in his or her sole discretion, may schedule or hold additional conferences with the petitioner concerning the factual allegations contained in the petition.

(d) Based solely on his or her discretion, the Secretary will determine whether to grant such a waiver or reduction. Pursuant to the procedure described in § 2570.83(b), the petitioner will be served with a written determination informing him or her of the Secretary's decision. Such written determination shall briefly state the grounds for the Secretary's decision, and shall be final and non-reviewable. In the case of a determination not to waive, the payment period for the penalty in question, if previously initiated, will resume as of the date of service of the Secretary's written determination.

§ 2570.86 Reduction of Penalty by Other Penalty Assessments.

The penalty assessed on a person pursuant to this section with respect to any transaction shall be reduced by the amount of any penalty or tax imposed on such person with respect to such transaction under ERISA section 502(i) and section 4975 of the Code. Prior to a reduction of penalty under this paragraph, the person being assessed must provide proof to the Department of the payment of the penalty or tax and the amount of that payment. Submissions of proof of other penalty or tax assessments will not toll the 60 day payment period, if previously initiated.

§ 2570.87 Revision of assessment.

If, based on the procedures described in §§ 2570.84, 2570.85, or 2570.86, the assessed penalty amount is revised, the person being assessed will receive a revised notice of assessment and will be obligated to pay the revised assessed penalty within the relevant 60 day payment period (as determined by the applicable procedure in §§ 2570.84, 2570.85, or 2570.86), and, if necessary, any excess penalty payment will be refunded as soon as administratively feasible. The revised notice of assessment will revoke any previously issued notice of assessment with regard to the transaction in question and will become a final order (within the meaning of 5 U.S.C. 704) the later of the first day following the 60 day payment period or the date of its service on the person being assessed, pursuant to the service procedures described in § 2570.83(b).

§ 2570.88 Effective Date.

This section is effective June 20, 1990 and shall apply to assessments under section 502(l) made by the Secretary after June 20, 1990 based on any breach or violation occurring on or after December 19, 1989.

Signed at Washington, DC, this 11th day of June, 1990.

David George Ball,

Assistant Secretary for Pension and Welfare Benefits, U.S. Department of Labor.

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