DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 333

[Docket No. 76N-0482]

Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Tentative Final Monograph

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) topical first aid antibiotic drug products are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Topical Antimicrobial II Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs on the proposed regulation by September 7, 1982. New data by July 11, 1983. Comments on the new data by September 9, 1983. 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). Written comments on the agency's economic impact determination by November 8, 1982.

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

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of April 1, 1977 (42 FR 17642), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC topical antibiotic drug products, together with the recommendations of the Advisory Review Panel on OTC Topical Antimicrobial II Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by June 30, 1977. Reply comments in response to comments filed in the initial comment period could be submitted by August 1, 1977.

In a notice published in the **Federal Register** of March 21, 1980 (45 FR 18400), the agency advised that it had reopened the administrative record for OTC topical antibiotic drug products to allow for consideration of data and information that had been filed in the Dockets Management Branch after the date the administrative record previously had officially closed. The agency concluded that any new data and information filed prior to March 21, 1980 should be available to the agency in developing a proposed regulation in the form of a tentative final monograph.

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

The advance notice of proposed rulemaking, which was published in the **Federal Register** of April 1, 1977 (42 FR 17642), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the present document is designated in the OTC drug review regulations as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule) the FDA states for the first time its position on the establishment of a monograph for OTC topical first aid antibiotic drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC topical first aid antibiotic drug products.

In response to the advance notice of proposed rulemaking, one drug manufacturer association, three drug manufacturers, two medical associations, nine physicians, one pharmacologist, one consumer, and one consumer group submitted comments. Copies of the comments received are also on public display in the Dockets Management Branch.

This proposal to establish new Subpart B of Part 333 constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC topical antibiotic drug products as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report. Modifications have been made for clarity and regulatory accuracy and to reflect any new information that has come to the agency's attention. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them.

The agency points out that the categories "skin wound protectant" and "skin wound antibiotic," as recommended by the Panel, have been replaced by the category "First aid antibiotic" and that a new Category I indication is proposed in this tentative final monograph. The details of these monograph modifications are explained in part I. paragraph B. 5. below—Comments on Product Categories and Labeling. The agency invites specific comment on these modifications.

In the **Federal Register** of September 13, 1984 (39 FR 33103), the agency published an advance notice of proposed rulemaking to establish a monograph for OTC topical antimicrobial drug products (21 CFR Part 333) in four subparts: Subpart A—General Provisions, Subpart B—Active Ingredients, Subpart C—Testing Procedures, and Subpart D—Labeling. In the **Federal Register** of January 6, 1978 (43 FR 1210), the agency published a tentative final monograph which contained the same subpart designations in Part 333 as described above. The agency is republishing Part 333 to delete the four subparts appearing in the tentative final monograph at 43 FR 1246. The sections appearing those subparts (§§ 333.1, 333.3, 333.20, 333.30, 333.40, 333.45, 333.50, 333.65, 333.80, 333.85, 333.87, 333.90, 333.92, 333.93, 333.97, 333.99) will now be combined under the designation "Subpart A—[Reserved]." The name of Subpart A has not yet been determined, but will be designated when that portion of Part 333 is republished as an amended tentative final monograph.

In the **Federal Register** of April 1, 1977 (42 FR 17642), the agency published an advance notice of proposed rulemaking to establish a monograph for OTC topical antibiotic drug products (21 CFR Part 342). The agency has determined that both antimicrobial and antibiotic drug products should be

combined into one monograph to be designated as "PART 333—Topical Antimicrobial Drug Products for OTC Human Use." Therefore, the proposed rulemaking for OTC Topical Antibiotic Drug Products (formerly designated as 21 CFR Part 342) will now be designated in this tentative final monograph as Subpart B of Part 333.

FDA published in the **Federal Register** of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy,* 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision is now deleted from the regulations. The regulations now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process, before the establishment of a final monograph (46 FR 47738).

Although it was not required to do so under *Cutler,* FDA will no longer use the terms "Category I," "Category II," and "Category III," at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the 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 products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved new drug application. Further, any OTC drug products subject to this monograph that are repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In the advance notice of proposed rulemaking for OTC topical antibiotic drug products (published in the **Federal Register** of September 13, 1974 (42 FR 17642)) the agency suggested that the conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the **Federal Register** and that the conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of whether further testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and if further reformulation is required, there could be a further delay in having a new product available for manufacture.

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the **Federal Register.** The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and have their products in compliance in the marketplace. However, if the agency determines that any labeling for a condition included in the final monograph should be implemented sooner, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular monograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call for data notice published in the **Federal Register** of September 7, 1973 (38 FR 24391) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

I. The Agency's Tentative Conclusions on the Comments and Reply Comments

A. General Comments

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

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products, published in the **Federal Register** of May 11, 1972 (37 FR 9464) and in paragraph 3 of the preamble to the tentative final monograph for antacid drug products, published in the **Federal Register** of November 12, 1973 (38 FR 31260). FDA reaffirms the conclusions stated there. Subsequent court decisions have confirmed the agency's authority to issue substantive regulations by rulemaking. See, e.g., *National Nutritional Foods Association* v. *Weinberger,* 512 F. 2d 688, 696–98 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers* v. *FDA,* 487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd,* 637 F. 2d 887 (2d Cir. 1981).

2. One comment contended that Category III is illegal and that consumers should not be exposed to antibiotics which have not been proven safe and effective while manufacturers undertake tests.

As noted earlier in this document, the legality of Category III was the subject of litigation in *Cutler* v. *Kennedy,* 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug regulations (21 CFR 330.10) were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, FDA proposed in the **Federal Register** of May 13, 1980 (45 FR 31422) to delete this provision and provide that any testing necessary to resolve safety or effectiveness issues that formerly resulted in a Category III

classification, and the 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.

The final rule on this proposal was published in the **Federal Register** of September 29, 1981 (46 FR 47730).

The agency points out that it has been FDA's policy to take regulatory action prior to a final monograph against products that present a potential health hazard or a significant and substantial question of effectiveness. The agency concludes that none of the topical antibiotics included in this document fit either of these criteria. Therefore, the agency sees no need for regulatory action on Category III conditions prior to the effective date of the final monograph for topical first aid antibiotic drug products.

3. Several comments supported the continued OTC availability of topical antibiotics for first aid of minor skin injuries. The comments stated that there is more evidence that topical antibiotics are safe and effective than for other topical antibacterial agents and that removing topical antibiotics from the OTC market would deprive the public of a safe and effective first aid product. The comments expressed concern that if OTC topical antibiotics were not available, the public would either switch to older, more toxic, and less effective OTC topical agents, such as ammoniated mercury, or delay proper first aid treatment until an infection developed and became severe enough to justify a visit to a physician.

Because the agency is not proposing to remove the entire topical antibiotic drug class from the OTC market, it is unnecessary to respond to the comment on a hypothetical basis. All OTC agents, including ammoniated mercury for topical use, are being reviewed and evaluated for safety and effectiveness. At the conclusion of the OTC drug review, only those ingredients that are generally recognized as safe and effective for OTC use will be included in the OTC drug monographs.

4. One comment expressed concern over the Panel's statement "that the American Academy of Pediatrics recommendations to the Panel (on the safety and effectiveness of certain OTC topical antibiotics) were based on members' (Academy members) clinical impressions rather than on a comprehensive review of the extensive data which was reviewed by the Panel." (See 42 FR 17646.) The comment submitted a statement concerning the effectiveness of topical antibiotics from the Academy's Committee on Drugs and pointed out that this statement, which was published in the June 1977 issue of *Pediatrics* (Ref. 1), represented the official position of the Academy. In this statement, the Academy concluded that the use of topical antibiotics may prevent infection after minor cuts, abrasions, and burns and therefore may be appropriate as an adjunct to cleansing, but it pointed out that systemic therapy is the treatment of choice in established skin infection. The Academy cautioned that because persons who are sensitive to neomycin may also react to other aminoglycosides (e.g., gentamycin, kanamycin, paromomycin, and streptomycin), the systemic use of any of the aminoglycoside antibiotics should be avoided, if possible, in patients known to be sensitive to neomycin. The Academy also cautioned that, because of possible absorption and systemic toxicity, aminoglycosides should not be used topically on large denuded skin surfaces.

The Panel's conclusion that the Academy's recommendations on the safety and effectiveness of certain topical antibiotics were based at that time on clinical impressions resulted from the appearance of a representative of the Academy at the Panel's meeting on July 24, 1975. The agency recognizes that the official statement of the Academy's Committee on Drugs was published in *Pediatrics* in June 1977 (Ref. 1) and was based on an extensive review of the literature. The agency has considered the Academy's official recommendations in reaching its conclusions on topical antibiotic drug products in this document.

Reference

(1) American Academy of Pediatrics Committee on Drugs, "Topical Antibiotics," *Pediatrics*, Supplement, 59:1041–1042, 1977.

B. Comments on Product Categories and Labeling

5. Numerous comments objected to the Panel's recommendation of two different drug product categories (skin wound protectant and skin wound antibiotic) for the same antibiotic-containing topical drug products. Several comments pointed out that, although the two product categories contained the same ingredients, the Panel recommended two different claims depending on whether a manufacturer chose to promote the product as a skin wound protectant or a skin wound antibiotic. The comments stated that there is no logical justification for two simultaneous categories for these antibiotic drugs.

Some of the comments contended that the Panel's definition of "skin wound protectant" is misleading, confusing, and scientifically unsound because it fails to recognize the antibacterial effects of topical antibiotics. The comments argued that unless the antibacterial effect of an antibiotic is to be acknowledged as more than an aid to the physical barrier effect of the product, there is no justification for adding it. The comments concluded that the skin wound protectant category should be eliminated from consideration in the labeling of OTC topical antibiotic drug products.

The agency agrees with the comments that the Panel's recommendation for two drug product categories for the same topical antibiotic ingredients, but with different labeling indications for each, would be confusing and misleading to consumers. The agency believes that the different claims can be appropriately classified in Categories I, II, or III within a single product category rather than having two separate drug categories for the different claims. Therefore, the agency proposed that there should be only one drug category for OTC topical products containing antibiotics.

FDA further agrees with the comments that it would be misleading to allow marketing of an antibiotic-containing drug product without labeling that indicates the product has antimicrobial activity. For this reason, the agency has decided that the "skin wound protectant" category, as recommended by the Panel, is inappropriate for topical antibiotic ingredients because it does not recognize the antimicrobial activity of the antibiotic ingredients.

In determining the name of this drug category, the agency has considered all of the available data, the Panel's recommendations, and the labeling of existing products. In comparing the indications recommended by the Panel for skin wound protectants and skin wound antibiotics, the agency identified the phrase "first aid product" as common to both drug categories. "First aid" is also a term that is frequently included in the labeling of topical antibiotic drug products, is readily understood by consumers, and reflects the intended OTC use of these products. For these reasons, FDA proposes that the drug category and statement of identity for OTC topical drug products containing antibiotics should be "first aid antibiotic."

The agency has also reviewed the available data to determine the acceptable Category I claims for this drug category. As discussed in comment 14 below, the agency concludes that the application of topical antibiotics may

help prevent infection in minor skin injuries. The agency has therefore determined that the Category I indication for a first aid antibiotic drug product should be as follows: "First aid to help prevent infection in minor cuts, scrapes, and burns." In order to improve clarity and to simplify OTC labeling, the agency has used the word "scrapes" instead of "abrasions" in the indication. The agency believes that this statement will clearly inform consumers of the function of these products.

In addition, the agency has reviewed the labeling recommended by the Panel in § 342.52(a) and proposes that those statements, with slight modifications or deletions made for clarity or to eliminate redundancy, may be used in addition to the required indication stated above. The revised labeling appears in § 333.150(b)(2) of this tentative final monograph as follows:

(1) (Select one of the following: "Decreases" or "Helps reduce") "the number of bacteria on the treated area."

(2) "Helps" (select one of the following: "prevent," "guard against," or "protect against") "skin infection."

(3) "Helps reduce the" (select one of the following: "risk" or "chance") "of skin infection."

(4) "Helps prevent bacterial contamination in minor cuts, scrapes, and burns."

In addition to the required indications the labeling may contain one or both of the following statements: "First aid product" or "Antibiotic medication for minor cuts, scrapes, and burns," provided such statements are neither placed in direct conjunction with information required to appear in the labeling nor occupy labeling space with greater prominence or conspicuousness than the required information.

Also, as discussed in comment 13 below, the agency proposes that treatment of infections is not an OTC indication, and such claims have been placed in Category II in this document.

The agency recognizes that the vehicles of topical antibiotic preparations contain many of the same ingredients that were reviewed as skin protectants by the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products (hereafter referred to as the Topical Analgesic Panel). The agency believes that any protection-type claims would be attributable to these ingredients and not to the antibiotic ingredients. The agency is also aware of substantial comment to the Topical Analgesic Panel's report on Skin Protectant Drug Products for Over-the-Counter Human Use, published in the Federal Register of August 4, 1978 (43 FR 34628), stating that skin protectants should not be considered drugs.

Because the subject of this document is topical first aid antibiotics and not protectants, the agency has deferred discussion of protective claims to the skin protectant rulemaking. Depending upon the agency's conclusions with regard to the advance notice of proposed rulemaking to establish a monograph for OTC skin protectant drug products, the agency will consider the suitability of a combination first aid antibiotic/skin protectant product and will amend the first aid antibiotic monograph at that time if necessary.

6. One comment believed that the Panel's distinction between antiseptics (which are often synthetic chemicals having antimicrobial actiyity when used in fairly high concentration) and antibiotics (chemicals which are derived from microorganisms and which have antimicrobial activity in low concentration) presents a problem because some antibiotics are now synthesized in commercial quantities.

The agency points out that the terms "antibiotic" and "antiseptic" are defined in the Federal Food, Drug, and Cosmetic Act (hereafter referred to as the act). An antibiotic drug is defined in section 507(a) of the act (21 U.S.C. 357(a)) as "any drug intended for use by man containing any quantity of any chemical substance which is produced by a microorganism and which has the capacity to inhibit or destroy microorganisms in dilute solution (including the chemically synthesized equivalent of any such substance)." Antiseptic is defined in section 201(o) of the act (21 U.S.C. 321(o)) as "* * * a germicide except in the case of a drug purporting to be, or represented as, an antiseptic for inhibitory use as a wet dressing, ointment, dusting powder, or such other use as involves prolonged contact with the body." The agency believes that the Panel was attempting to distinguish the antibiotic class of drugs from other (nonantibiotic) antimicrobial drugs. Antibiotics are all produced by or derived from living microorganisms even though, as the comment states and the act recognizes, some are now being commercially synthesized. Nonantibiotic antimicrobial drugs are chemically synthesized and are usually used in higher concentration.

The agency believes that the term "antiseptic" is most often associated with the nonantibiotic group of antimicrobial drugs and that allowing this term to be used on antibiotic products would be misleading and confusing to consumers. For this reason, the agency agrees with the Panel that the term "antiseptic" is a Category II claim for topical antibiotic drug products. The agency further believes that the term "first aid antibiotic," discussed in comment 5 above, adequately identifies this class of OTC drug products and distinguishes it from other antimicrobial products.

7. One comment contended that FDA does not have the authority to legislate the exact wording of OTC labeling claims to the exclusion of what the comment described as other equally truthful claims for the products. The comment objected to the labeling recommended by the Panel as being overly restrictive and recommended that more flexibility in labeling be permitted by adding the following statement to each list of approved claims: "* * * or similar indication statements which are in keeping with the Panel's report." The comment further contended that some of the wording recommended by the Panel is meaningless to consumers and suggested that manufacturers be permitted to use those words that experience indicates are best understood by consumers. Specifically, the comment questioned what meaning the terms "hand eczema," "wound contamination," "protectant," and "microorganisms" would have to the consumer.

Since the inception of the OTC drug review, the agency has maintained that a monograph describing the conditions under which an OTC drug will be generally recognized as safe and effective and not misbranded must include both specific active ingredients and specific labeling. (This policy has become known as the "exclusivity rule.") The agency's position has been that it is necessary to limit the acceptable labeling language to that developed and approved through the OTC drug review process in order to ensure the proper and safe use of OTC drugs. The agency has never contended, however, that any list of terms developed during the course of the review literally exhausts all the possibilities of terms that appropriately can be used in OTC drug labeling. Suggestions for additional terms or for other labeling changes may be submitted as comments to proposed or tentative final monographs within the specified time periods or through petitions to amend monographs under 21 CFR 330.10(a)(12). For example, the labeling proposed in this tentative final monograph has been expanded and revised in response to comments received.

During the course of the review, FDA's position on the "exclusivity rule"

has been questioned many times in comments and objections filed in response to particular proceedings and in correspondence with the agency. The agency has also been asked by the Proprietary Association to reconsider its position. To assist the agency in resolving this issue, FDA plans to conduct an open public forum on September 29, 1982 where all interested parties can present their views. The forum will be a legislative type administrative hearing under 21 CFR Part 15 that will be held in response to a request for a hearing on the tentative final monograph for nighttime sleep aids (published in the **Federal Register** of June 13, 1978; 43 FR 25544). Details of the hearing were announced in a notice published in the **Federal Register** of July 2, 1982 (47 FR 29002). In proposed and tentative final monographs issued in the meantime, the agency will continue to state its longstanding policy. Accordingly, the agency at this time does not accept the comment's recommendation to add to the monograph the statement "* * * or similar indications statements which are in keeping with the Panel's report."

FDA believes that the labeling of OTC antibiotic drug products has been made clearer and more meaningful to the consumer by the changes reflected in this document. These changes include the deletion of the terms "microorganisms," "protectant," and "hand eczema," three of the four terms which the comment contended consumers would not understand. (See comment 8 below for discussion of "hand eczema.") "Wound contamination," the fourth term, has been revised to "bacterial contamination in minor cuts, scrapes, and burns" in the following allowable statement in § 333.150(b)(2)(iv): "Helps prevent bacterial contamination in minor cuts, scrapes, and burns." As discussed above, labeling terminology in addition to that specified in the monograph can still be considered when a final monograph is issued.

8. One comment questioned whether most consumers would know what the term "hand eczema" means. This term appears in the Panel's warning, "Do not use on long-standing skin conditions such as leg ulcers, diaper rash or hand eczema," in §§ 342.50(b)(5) and 342.52(b)(5).

The agency agrees that most consumers probably would not know what the term "hand eczema" means. The agency believes that the use of this term in the above warning is confusing because it implies that an OTC topical antibiotic may be used on eczema that occurs on areas of the body other than the hands. The agency concludes that it was the Panel's intent to prohibit the use of OTC topical antibiotics on any chronic skin condition, including eczema on any part of the body. The agency believes that the revised indication for use, "first aid to help prevent infection in minor cuts, scrapes, and burns," and the 1-week use limitation warning are sufficient to warn the consumer that topical antibiotics are not to be used on longstanding skin conditions. Therefore, the Panel's warnings in §§ 342.50(b)(5) and 342.52(b)(5) have been deleted from the monograph. The agency recognizes, however, that a physician may prescribe an OTC topical antibiotic to be used for longer than 1 week. For this reason, the 1-week use limitation warning has been revised to read as follows: "Do not use longer than 1 week unless directed by a doctor."

9. One comment stated that the labeling of topical antibiotic drug products should be clear and simple, and that the agency should limit the number of explicit instructions to avoid confusion or causing the consumer needless anxiety.

Another comment expressed concern over the extensive warnings recommended by the Panel. The comment pointed out that the length and extent of these warnings may be counterproductive because the consumer may not pay attention to important warning statements and may become unduly alarmed and confused. The comment recommended that FDA accept only those warnings that are necessary and meaningful to consumers.

The agency agrees that the labeling of all OTC drug products should be understandable to the public and should include only those directions and warnings that are necessary for the safe and effective use of the product. While the comments failed to indicate which statements are not clear and simple or which warnings would confuse or needlessly alarm the consumer, the agency points out that a number of changes have been made in the Panel's recommended labeling. For example, in the response to comment 5 above, the agency discusses its decision to make substantial changes in the definitions of product categories of topical antibiotics, and these changes are reflected in the labeling.

For clarity and to eliminate some duplicative words, the agency has combined and revised the warnings in § 342.50(b)(1), (4), and (5) to read as follows: "For external use only. Do not use in the eyes or apply over large areas of the body. In case of deep or puncture wounds, animal bites, or serious burns, consult a doctor." The agency has added "animal bites" to this warning, although such injuries might be included under "puncture wounds." However, the agency believes that many consumers may not consider animal bites as puncture wounds. In order to assure that the warning is clear, the term "animal bites" has been added because it is understood by all consumers. Animal bites often become infected, and consumers should be alerted to get proper medical care.

The agency has combined and revised the warnings in § 342.50(b)(2) and (3) to read as follows: "Stop use and consult a doctor if the condition persists or gets worse. Do not use this product longer than 1 week unless directed by a doctor." The agency believes that the warning recommended by the Panel in § 342.50(b)(3) could confuse consumers because it states that the user should stop using the product if itching, redness, swelling, or pain develops or increases. These are the same symptoms that often occur after a minor skin injury, the condition for which topical first aid products are indicated. The agency believes that the above revision will be more informative and less confusing to consumers.

The agency has also slightly revised the directions for use to make them clearer. (See comments 7 and 8 above for other specific labeling changes.)

10. One comment suggested deletion of the Panel's recommended warning in § 342.52(b)(2), "Do not use longer than 1 week." The comment claimed that the desired effect of the warning could be achieved by adding the words "for not longer than 1 week" to the last sentence in the directions for use in §§ 342.50(c) and 342.52(c), to read as follows: "May be applied one to three times daily for not longer than 1 week."

The agency disagrees with the comments The purpose of a period-of-use statement on a product is to warn the consumer of the product's limitations. In the case of OTC topical antibiotics, the indications are for minor cuts, scrapes, and burns, which normally heal within 1 week. If the 1-week limitation statement were incorporated into the directions for use, it would lose its intended effect of alerting consumsers that an unhealed lesion could indicate a more serious skin disease or a proliferating infection. Therefore, the agency proposes that the 1-week limitation, as modified in comment 8 above, be retained as part of the warnings.

11. One comment objected to the Panel's Category II classification of

labeling terms that suggest decreased healing time. The comment maintained that the Panel's statement that the rate of wound healing may vary, depending on how many and what types of bacteria are present in the wound, and the Panel's conclusion that there is little evidence to support the claim of shortened healing time are inconsistent. The comment also pointed out that the Panel should not have been concerned with wound-healing claims because under § 369.21 (21 CFR 369.21) topical antibiotic drug products containing the bacitracin-polymyxin-neomycin combination may be labeled only for the prevention of infection in minor cuts and abrasions. The comment stated that § 369.21 would prevent claims dealing with wound healing from being used in the labeling of these products; therefore, the Panel's statement that manufacturers had made such claims was incorrect.

The agency agrees with the Panel that the rate of healing is variable, depending on the number and types of bacteria present in the wound. However, the Panel placed wound-healing claims in Category II because it had no evidence to show that applying topical antibiotics to minor wounds would alter the healing rate. The agency agrees that additional evidence is necessary to support such claims. Although § 369.21 indicates that any bacitracin-containing preparation is to be labeled only for the prevention of infection in minor cuts and abrasions, several marketed products submitted to the Panel for review (Ref. 1 through 6) included the indications "aids in healing" or "as an aid to healing." It was for this reason that the Panel categorized these claims. The agency points out that the current regulations for labeling topical antibiotics in § 369.21 will be revoked on the effective date of the final monograph for OTC first aid antibiotics.

References

(1) OTC Volume 190001.
(2) OTC Volume 190003.
(3) OTC Volume 190004.
(4) OTC Volume 190005.
(5) OTC Volume 190008.
(6) OTC Volume 190012.

12 Two comments objected to the Panel's Category II classification of the phrase "helps kill bacteria." One comment noted that the Panel acknowledged in its discussion on potencies that each antibiotic ingredient is present in products in sufficient amounts to either destroy susceptible bacteria or arrest their development. The other comment questioned the logic of prohibiting the phrase "kills bacteria" but permitting the phrase "decreases bacteria," when the mechanism by which the bacteria are "decreased" is by "killing" them.

The agency agrees with the Panel's Category II classification of the phrase "helps kill bacteria," although for different reasons than those stated by the Panel. According to the definition in section 507(a) of the act (21 U.S.C. 357(a)), antibiotics have the capacity to inhibit or destory microorganisms. However, the agency believes that the claim "helps kill bacteria" is misleading to the average consumer because the word "kill" implies elimination of all bacteria on the skin when, in fact, topical antibiotics only decrease the number of certain bacteria on the skin. For this reason, the ageny believes that the term "decreases the number of bacteria" would not be misleading and is an allowable Category I labeling claim. (See comment 5 above.) The phrase "helps kill bacteria" will remain in Category II.

13. One comment objected to the Panel's conclusion that the claim "treats infection" would be acceptable for OTC labeling of topical antibiotics provided that the effectiveness of this claim was established in controlled studies. The comment pointed out that OTC topical antibiotic drug products are now labeled principally for prevention of infection on the premise that lay users could properly use a topical antibiotic only for prevention of infection.

The agency agrees with the comment that treatment of bacterial skin infection is not an OTC indication. Lay persons do not have adequate medical background or training and should consult a physician for diagnosis and appropriate therapy of the different types of skin infections. Also, the treatment of bacterial infections usually involves systemic therapy. Therefore, the agency concludes that the claim "treats infection" or any similar claim is inappropriate for OTC first aid antibiotic drug labeling and is classified Category II. However, the agency would consider including claims for treatment of skin infection in professional labeling if data are submitted to demonstrate the effectiveness of topical first aid antibiotics for this use.

C. Comments on Effectiveness of Topical Antibiotics

14. One comment, opposed to the availability of OTC topical antibiotics, asserted that consumers should not be exposed to any topical antibiotic for the prevention of minor skin infections. The comment stated that there is little chance of minor cuts and wounds becoming infected and that such infections are usually handled by the body's normal healing functions. The comment concluded that even if topically applied antibiotics are shown to be effective in preventing infection, the risks would outweigh the benefit. These risks include the possibility of sensitization of the skin, or the development of bacterial resistance to other antibacterial agents that might be important for treating serious disease.

A reply comment agreed that many minor skin injuries heal without treatment, but pointed out that some do not and that it is impossible to make a distinction at the time of injury. This comment stated that most people want to insure against the risk of infection by applying a safe and effective product for that purpose.

Other comments stated that OTC topical antibiotics can provide rational preventive therapy. Several comments objected to the Panel's not accepting controlled studies of prevention and treatment of infection in large wounds. The comments contended that if an antibacterial preparation is effective in reducing the incidence of infection in a variety of large wounds, there is no reason to believe that the same activity would not be exerted in smaller wounds.

One comment, noting that FDA has provided for a waiver from the requirement of controlled clinical trials for OTC drugs (21 CFR 330.10(a)(4)(ii)), objected to the Panel's unwillingness to apply this waiver to the topical antibiotic ingredients (42 FR 17647). The comment concluded that topical antibiotics have been used for 25 years, and that this experience is sufficient to support the continued use of these products in the prevention and treatment of minor skin injuries.

The agency has determined that OTC topical antibiotic drug products can be used safely and effectively to help prevent infection in minor skin injuries. The agency concludes that this use of the OTC topical antibiotics is rational and dose not pose undue risks to the consumer.

The agency agrees with the comments that many minor skin injuries, such as cuts and scrapes, are self-healing and that the body's healing mechanisms can handle some infections that might develop in these injuries. However, as the reply comment pointed out, some minor skin injuries do not heal without treatment and it is impossible to make this distinction at the time of injury.

The agency believes that reducing the number of bacteria on the skin may help prevent infection in minor skin injuries. It is well documented in the medical literature that applying topical antibiotics to skin wounds reduces the

number of bacteria at the site of application and serves as an adjunct to cleansing wounds (Refs. 1 through 4). The agency also agrees with the Panel that studies in which topical antibiotics were used in major wounds under supervised conditions in hospitals or physicians' offices (Refs. 5 through 9) were insufficient to establish the prophylactic effectiveness of topical antibiotics in minor skin injuries, and that a well-controlled study of the prophylactic effectiveness of these drug products on minor skin injuries was needed.

The agency has reviewed a well-controlled study, published after the Panel had completed its review, in which the effectiveness of an antibiotic ointment was compared with a placebo in preventing infection in minor skin injuries and insect bites (Ref. 10). This 15-week study was conducted in a rural day-care center in 59 subjects ranging in age from 2 through 5 years. Health aides examined the children daily for minor skin injuries or insect bites, and a placebo ointment or an ointment containing neomycin sulfate, zinc bacitracin, and polymyxin B sulfate was applied three times daily to any minor skin injury or insect bite. Minor skin injuries and insect bites occurred with similar frequency in both treatment groups.

The study investigators examined the children twice weekly and cultured lesions that were present at either or both of these examinations. Epidermal cultures were done weekly. Fifteen (47 percent) of the 32 children in the placebo group and 3 (15 percent) of the 27 children in the antibiotic group developed streptococcal infection. Infections recurred in five of the placebo group but none of the antibiotic group. Twelve children in the placebo group and one child in the antibiotic group required oral therapy for the skin infection. The authors stated that the lower incidence of streptococcal skin infection in the antibiotic group was statistically significant ($p < 0.01$).

The agency considers this study, along with the other data cited above, as sufficient evidence to support the claim "first aid to help prevent infection in minor cuts, scrapes, and burns" for all OTC topical antibiotics. Treatment of infection is not appropriate as an indication for OTC topical antibiotics. (See comment 13 above.)

References

(1) Leyden, J. J., R. Stewart, and A. M. Kligman, "Updated *in vivo* Methods for Evaluating Topical Antimicrobial Agents on Human Skin," *The Journal of Investigative Dermatology*, 72:165–170, 1979.

(2) Marples, R. R., and A. M. Kligman, "Methods for Evaluating Topical Antibacterial Agents on Human Skin," *Antimicrobial Agents and Chemotherapy*, 5:323–329, 1974.

(3) Marples, R. R. A. Rebora, and A. M. Kligman, "Topical Steroid-Antibiotic Combinations: Assay of Use in Experimentally Induced Human Infections," *Archives of Dermatology, 108:237–240, 1973.*

(4) Leyden, J. J., and A. M. Kligman, "Rationale for Topical Antibiotics," *Cutis*, 22:515–528, 1978.

(5) Mack, R. M., and J. R. Cantrell, "Quantitative Studies of the Bacterial Flora of Open Skin Wounds: The Effect of Topical Antibiotics," *Annals of Surgery*, 166:886–896, 1967.

(6) Reiss, E., and E. J. Pulaski, "Local Antibiotics in Established Wound Suppuration," *Surgical Forum*, 1951:539–543, 1951.

(7) Saik, R. P., C. A. Walz, and J. E. Rhoads, "Evaluation of a Bactracin-Neomycin Surgical Skin Preparation," *American Journal of Surgery*, 121:557–560, 1971.

(8) Stone, H. R., and R. Hester, "Incisional and Peritoneal Infection after Emergency Celiotomy," *Annals of Surgery*, 177:669–677, 1973.

(9) Levy, R. S., J. Goldstein, and R. S. Pressman, "Value of a Topical Antibiotic Ointment in Reducing Bacterial Colonization of Percutaneous Venous Catheters," *Journal of the Albert Einstein Medical Center*, 18:67–70, 1970.

(10) Dillon, H. C., S. Maddox, and J. C. Ware, "Pathogenesis and Prevention of Streptococcal Impetigo," *in* "Current Chemotherapy and Infectious Disease—Proceedings of the 11th International Congress of Chemotherapy and the 19th Interscience Conference on Antimicrobial Agents and Chemotherapy," The American Society for Microbiology, Washington, Vol. II, pp. 1190–1192, 1980.

15. Two comments stated that OTC topical antibiotics applied to an insect bite or a wound are capable of killing the bacteria that would go on to produce impetigo in susceptible populations. One comment stated that application of topical antibiotics to impetigo lesions serves as an adjunct ot systemic therapy by minimizing the shedding of virulent organisms into the environment because systemic antibiotics do not reach the outer surfaces of skin lesions. The comment cited a published article (Ref. 1) to support this statement.

The agency has reviewed the article cited by the comment. The authors of the article discussed the potential use of topical antibiotics as adjuncts to systemic therapy by reducing the shedding of virulent organisms into the environment. The study was not designed to evalute this indication, but rather to evaluate the effectiveness of antibiotic combinations in experimentally induced infections. In addition, the authors concluded that a final judgment on the usefulness of topical antibiotics in prevention the shedding of virulent organisms into the environment would depend upon evidence of clinical efficacy. The agency concurs with the authors' conclusions. (For a discussion of the effectiveness of topical antibiotics in preventing infection in minor skin injuries, see comment 14 above).

Reference

(1) Marples, R. R., A. Rebora, and A. M. Kligman, "Topical Steroid-Antibiotic Combinations. Assay of Use In Experimentally-Induced Human Infections," *Archives of Dermatology*, 108:237–240, 1973.

16. Several comments suggested using a human model study as an alternative to the Panel's recommendation of a double-blinded, controlled clinical study to substantiate claims for prevention and treatment of infection for topical antibiotics. The comments stated that the following difficulties are likely to occur in performing a clinical study using patients with spontaneously occurring wounds: (1) Variability in the extent and depth of spontaneous lesions; (2) differences in the age of the lesion at the time the treatment is started; (3) differences in the number and type of organisms causing the infection; (4) differences from one patient to another in response to infection, personal habits, and living environment. The comments concluded that these difficulties could be avoided by using a human model study in which these factors are more exactly controlled.

Several comments considered it unethical to withhold antibacterial treatment from patients randomly selected for a clinical trail because of the potential for septicemia or acute poststreptococcal glomerulonephritis developing. One comment stated that a human model study on healthy young adult volunteers would use accurately determined numbers of known pathogenic staphylococci and streptococci, and care would be taken to avoid using strains of streptococci that can cause poststreptococcal glomerulonephritis to develop.

One comment stated that the Panel's report contained several substantive errors regarding published work, unpublished material, and testimony to the Panel concerning human model studies. The comment resubmitted a protocol for a human model study (Ref. 1) and stated that this particular model had used *Staphylococcus aureus* and a pathogenic strain of *Escherichia coli*, and not normal skin bacteria as the Panel stated. The comment contended

that the Panel's recommended requirement that "effectiveness must necessarily be demonstrated in clinical trails because this model system uses normal skin bacteria" is not a valid conclusion. (See 42 FR 17650.)

The comments concluded that well-controlled human model studies, using volunteers, were submitted to the Panel to show that bacitracin and polymyxin, alone and in combination, are effective in preventing infection in experimentally induced wounds. The comments objected to the Panel's Category III classification of the claim "prevents infection" for the combination of bacitracin and polymyxin B sulfate.

The agency disagrees with the comments that the performance of clinical trials to study prevention and treatment claims is unethical. Although septicemia can develop from minor cuts or scrapes, it is extremely rare. Testimony presented to the Panel during its deliberations showed that treatment probably cannot be administered soon enough to prevent glomerulonephritis when a nephritogenic strain is present in an infection. (A nephritogenic strain of streptococci is one that can cause inflammation of the kidney.). Therefore, the risk of poststreptococcal glomerulonephritis would not differ between the treated and the control groups in the clinical trial.

As discussed previously, claims of preventing bacterial infection are Category I (see comments 5 and 14 above); claims of treating bacterial infections are Category II (see comment 13 above). The agency points out that the combination of bacitracin and polymyxin B sulfate is Category I for the indication "first aid to help prevent infection in minor cuts, scrapes, and burns," and needs no further study. (See § 333.110 and § 333.120 in this tentative final monograph.)

The agency believes that human model studies have a place in the testing of topical antibiotics. For example, they can be used as a screening mechanism to determine the possible effectiveness of new ingredients or to demonstrate bioavailability of the Category I ingredients from new formulations. However, because the agency has reclassified most of the submitted antibiotics into Category I, there is no need to discuss model studies in great detail in this document.

Reference

(1) Comment No. 00005, Docket No. 76N–0482, Dockets Management Branch.

17. One comment contended that the Panel's conclusion that topical antibiotics have not been shown to prevent or treat infections was influenced by the results of a study performed in 1971 (Ref. 1), and this study has since been discredited. This study compared the effectiveness of a bacitracin, polymyxin, and neomycin combination with the base alone in 30 patients with impetigo. On each patient one lesion was treated with the combination antibiotic preparation, and another lesion was treated only with the base, on the assumption that each person would serve as his or her own control. Although treated and untreated lesions showed some improvement, no significant differences were reported between the effects of the antibiotic and the placebo.

The comment argued that the phenomenon of translocation (the spread of a drug from the site of application to other areas of the skin) operated to produce an antibiotic effect on both lesions of each subject because the lesions were deliberately left uncovered after the ointments were applied. The comment contended that because this study met the Panel's recommendations for control, it influenced the Panel's final conclusions, even though a report on translocation (Ref. 2) was included in a submission to the Panel in 1975 (Ref. 3).

The agency notes that the summary of data and conclusions in this submission has since been published (Ref. 4). The agency agrees with the comment that the phenomenon of translocation could explain the results of the 1971 study cited by the Panel. However, a more involved discussion of this issue is not necessary because FDA has placed prevention claims in Category I and treatment claims in Category II. (See comments 5, 13, and 14 above.) Also, according to § 333.120, the combination of bacitracin, polymyxin, and neomycin is Category I.

References

(1) Pace, B. F., "Report on Mycitracin-Impetigo Study," Draft of unpublished paper in OTC Volume 190023.

(2) Marples, R. R., and A. M. Kligman, "Limitations of Paired Comparisons of Topical Drugs," *British Journal of Dermatology*, 88:61–67, 1973.

(3) OTC Volumes 190019 through 190025.

(4) V. Anderson, "Over-the-Counter Topical Antibiotic Products Data on Safety and Efficacy," *International Journal of Dermatology*, Supplement, 15:1–118, 1976.

18. One comment objected to the Panel's recommendation that animal and human model studies be used to test the effectiveness of the submitted antibiotic ingredients because of the large volume of clinical experience already at hand. The comment pointed out that such studies are suitable for screening new ingredients before clinical trials, but are unnecessary and wasteful for widely used ingredients.

As stated in comment 16 above, the agency agrees that animal and human model studies are useful as a screening mechanism; however, they will not be required for establishing proof of the effectivenes of the submitted antibiotic ingredients. Because gramicidin is the only submitted ingredient that remains to be tested, and because it will not be necessary to test this ingredient using animal or human model studies, it is not necessary to discuss the use of these models any further in this document. Because no comments were received regarding gramicidin, the agency will address the testing of gramicidin in response to any future comments as provided in the policy statement published in the **Federal Register** on September 29, 1981 (46 FR 47740).

D. Comments on Safety of Topical Antibiotics

19. Several comments objected to the Panel's concern over potential misuse of OTC topical antibiotics because the Panel had no evidence that these products had ever been misused. The comments contended that theoretical possibilities should not be made a part of a scientific report and that it was improper for any scientific Panel to assume "misuse" of the drugs under its purview.

FDA agrees that the Panel cited no specific evidence of misuse of OTC topical antibiotic ingredients. However, the agency does not agree that concerns about potential misuse should not be a part of a scientific report. Theoretical concerns of misuse or potential misuse may be taken into account by panels in determining general recognition of safety and in developing labeling for an OTC drug product. The Panel's main concern in considering this potential problem was to recommend labeling that would, through clear and accurate directions for use and warnings against misuse, prevent misuse or abuse of these products.

20. Several comments stated that preparations that are merely occlusive barriers (and do not contain an antibiotic) may be dangerous for the public to use on minor skin injuries because such products would be ineffective in preventing multiplication of bacteria and could even favor the proliferation of bacteria. These comments supported the continued availability of topical antibiotic drug products and stated that there is no justification for a skin wound protectant without antimicrobial action.

As stated in comment 14 above, the agency has concluded that topical antibiotics will continue to be available as OTC first aid preparations to be applied to minor cuts, scrapes, and burns to help prevent infection. The comments' argument that there is no justification for skin wound protectants without antimicrobial activity concerns a class of products that does not fall within the scope of this tentative final monograph. Products of this type were discussed by the Topical Analgesic Panel in the advance notice of proposed rulemaking for skin protectant drug products, which was published in the **Federal Register** of August 4, 1978 (43 FR 34628). The agency will address the issue of skin wound protectants without antimicrobial activity in a future issue of the **Federal Register.**

21. One comment objected to the following statement by the Panel concerning the data necessary to establish the safety of all topical antibiotics: "Studies should be conducted to determine the highest blood levels achievable in man from maximum exposure to topical application." (See 42 FR 17652.) The comment contended that such a study was conducted and presented to the Panel in May 1975 (Refs. 1 and 2), but the results of the study apparently were not taken into account in the Panel's conclusions.

The agency points out that the statement to which the comment objected is part of the Panel's general discussion of the rationale for determination of the safety factors of topical antibiotics and is not part of the Panel's recommended testing guidelines. Although the study cited by the comment was not specifically cited by the Panel in its report, the agency does not agree that its results were not taken into account. The agency points out that the Panel concluded that it had been presented with enough data on all ingredients except gramicidin to make a determination concerning systemic toxicity. The agency concurs with the Panel that no further systemic toxicologic data are needed for any of the submitted OTC topical antibiotics other than gramicidin. The agency encourages manufacturers to use the Panel's recommendations for guidance in the development of the toxicologic data necessary for establishing the safety of gramicidin when used topically. (See 42 FR 17678.)

References

(1) OTC Volumes 190019 through 190025.

(2) V. Anderson, "Over-the-Counter Topical Antibiotic Products: Data on Safety and Efficacy," *International Journal of Dermatology*, Supplement, 15:79–82, 1976.

22. One comment urged FDA to ban the prophylactic use of all topical antibiotics because such unnecessary exposure to antibiotics increases the chances of bacterial resistance to antibiotics that are useful or essential for the systemic treatment of serious infections. The comment contended that FDA has proposed to ban the use of certain antibiotics in animal feed because of the potential for promoting bacterial resistance, and that antibiotics for prevention of minor skin infections should be banned for the same reason.

The agency's proposal, published in the **Federal Register** of January 20, 1978 (43 FR 3023), was not intended to ban the use of all antibiotics in animal feed, but to limit the routine subtherapeutic use of certain antibiotics in animal feed. The proposal was based on the concern that chronic exposure to animal feeds containing antibiotics could lead to the development of antibiotic-resistant bacteria. However, the proposal was limited to those antibiotics that are also used systemically in humans to treat infections.

The agency points out that, for the most part, the antibiotics used in OTC topical first aid products are not used systemically. The agency recognizes that the use of topical antibiotics in closed environments, such as hospitals, or in chronic conditions for extended periods of time may lead to the development of resistant strains. However, the agency is unaware of any evidence indicating that the occasional use of OTC topical antibiotics has led to an increase in infection in the general population because of resistant organisms. Therefore, the agency concludes that concerns regarding the development of resistant organisms from occasional use of OTC topical antibiotics should not prevent these ingredients from being classified in Category I.

E. Comments on Bacitracin

23. One comment contended that products containing antibiotics effective only for gram-positive bacteria, such as bacitracin, may promote the uncontrolled growth of gram-negative bacteria and that the Panel failed to address this potential problem in its report. A reply comment maintained that the Panel recognized the potential for bacterial overgrowth and made recommendations in those cases where there was a problem, e.g., in recommending that polymyxin B sulfate should not be used as a single active ingredient in OTC antibiotic drug products.

The agency agrees with the reply comment that the Panel recognized the limited spectra of the various antibiotic ingredients (e.g., polymyxin B sulfate and bacitracin) and considered the potential for bacterial overgrowth if those ingredients were used alone. Polymyxin B sulfate is active against certain gram-negative bacteria, but is not active against gram-positive bacteria. Because most infections of minor skin wounds are caused by gram-positive bacteria, applying polymyxin B sulfate alone could allow for uncontrolled growth of these gram-positive bacteria. The Panel determined, and the agency agrees, that it is rational to require polymyxin B sulfate to be used only in combination with antibiotics that have activity against gram-positive bacteria. Conversely, because bacitracin is active against gram-positive bacteria, which are the most frequent cause of minor skin wound infections, the Panel determined that it is aceptable to use this ingredient alone as a first aid antibiotic. The agency also agrees with this conclusion.

F. Comments on Neomycin.

24. One comment contended that neomycin should be removed from the market immediately until it is proven safe and effective. The comment stated that the National Academy of Sciences—National Research Council Drug Efficacy Study concluded that topical applications of neomycin have not been proven effective. (See 37 FR 12857.) A reply comment stated that this study did not make that conclusion, but instead stated that no well-controlled trials comparing topical neomycin with the cream or ointment vehicle alone in minor skin infections have been reported.

The agency agrees with the reply comment that the Drug Efficacy Study concluded that neomycin preparations were possibly effective for their labeled indications, not that they were ineffective. The Drug Efficacy Study stated that many studies support the fact that superficial skin injuries and infections improve after the use of topical neomycin preparation; however, in searching the literature of 1952 to 1967, no double-blind, controlled studies comparing neomycin ointment or cream with the vehicle alone were found. The agency points out that any final conclusions on certain OTC topical preparations containing neomycin sulfate were deferred to the OTC drug review. A notice of this deferment was published in the **Federal Register** on

June 29, 1972 (37 FR 12857). As discussed below (see comments 25 through 28), the agency has reclassified neomycin sulfate from Category III to Category I.

25. Several comments objected to the Panel's classification of neomycin in Category III because the use of neomycin may promote the development of resistant organisms or cross-resistance to other aminoglycoside antibiotics. The comments stated that although cases of neomycin resistance and cross-resistance in closed environments, such as hospitals, have been reported, there is no evidence that the use of neomycin in the general population has led to any increase in infection due to neomycin-resistant strains. One comment stated that the Panel used a "double standard" in evaluating bacterial resistance of neomycin and the tetracyclines when it classified these topical antibiotics. The comment stated that bacterial resistance to tetracyclines has been demonstrated in hospitalized patients, but this did not prevent the Panel from classifying the tetracyclines in Category I.

The agency recognizes that the use of topical antibiotics in closed environments, such as hospitals, or in chronic conditions for extended periods of time has led to the emergence of resistant strains of bacteria. These closed environments are particularly prone to the development of resistant strains. However, the agency is unaware of any evidence indicating that the occasional use of OTC topical antibiotics, including neomycin, has led to an increase in infection in the general population because of resistant organisms. OTC topical antibiotics have been marketed for a number of years, some for more than 25 years. The agency believes that if the development of resistance were a problem from the OTC use of these ingredients it would have been evident by now. As noted in comment 22 above, the agency concludes that concerns regarding the development of resistant organisms for occasional use of OTC topical antibiotics should not prevent these ingredients from being classified in Category I.

26. One comment stated that until the Panel's questions concerning percutaneous absorption of neomycin are answered, it must be assumed that topical use of this ingredient presents the same risks of deafness and kidney damage that are seen from systemic use of the drug. Other comments objected to the Panel's statement that toxic blood levels can be reached if neomycin sulfate preparations are placed on large areas of broken skin (42 FR 17662), and that the amount of neomycin that may be absorbed into the bloodstream after topical application to diseased skin is unknown (42 FR 17661). One comment contended that the Panel's statements are imprecise because a study submitted to the Panel in May 1975, a summary of which has since been published (Ref. 1), showed that the use of neomycin in patients with widespread psoriasis and atopic dermatitis produced no detectable blood levels of neomycin despite the patients' broken skin barrier. Another comment pointed out that systemic toxicity has occurred only when neomycin has been applied to large areas of denuded skin, and that there is no risk of toxicity from the application of neomycin to minor cuts and burns.

Although FDA agrees with the comments that the Panel's statements regarding "broken" and "diseased" skin are imprecise, the agency believes that it was the Panel's intent to make it clear that the topical use of neomycin can be potentially hazardous if the drug is used improperly. After reviewing the Panel's report and the comments, the agency concludes that the short-term use of neomycin in minor cuts and burns would not present a toxicologic risk. The agency concurs with the Panel's conclusion that no further toxicologic testing is needed for neomycin for OTC topical use.

Reference

(1) Anderson V., "Over-the-Counter Topical Antibiotic Products: Data on Safety and Efficacy," *International Journal of Dermatology*, Supplement, 15:79–82, 1976.

27. Several comments objected to the Panel's placement of neomycin sulfate in Category III because of questions concerning this ingredient's sensitization potential. The comments contended that the symptoms of sensitization are not serious and that they subside and leave no lasting effect when the treatment is stopped. One of the comments submitted two articles (Refs. 1 and 2), which were published after the Panel had completed its deliberations. These articles show that the incidence of sensitivity is much lower than previously believed and that the topical use of neomycin products on minor cuts or abrasions presents little risk to the user. Another comment suggested that a precautionary statement on the label would be more appropriate than the testing recommended by the Panel to determine the sensitization rate of neomycin in the general population, because the frequency of clinical hypersensitivity to neomycin is probably quite low and because the reactions are not serious. Another comment stated that neomycin sulfate should not be available OTC because it can cause allergic sensitization and can sensitize the skin to structurally related, potentially lifesaving drugs.

After evaluating the comments and other information, the agency believes that little would be gained by requiring further study to determine the actual prevalence or incidence of neomycin sensitization in the general population. Therefore, no further testing to determine a sensitization rate will be required.

Among the studies reviewed by the agency was one by Leyden and Kligman (Ref. 1), in which 2,175 subjects were patch tested with 20 percent neomycin sulfate ointment. The researchers reported that only two subjects (0.09 percent of the total population) had a clear-cut reaction to neomycin. Both of these subjects had a history of frequent use of neomycin-containing products.

Leyden and Kligman (Ref. 1) also reviewed the results of patch testing with 20 percent neomycin in 653 children who had chronic dermatoses and had been referred for diagnostic patch testing. Only one child (0.15 percent) had an allergic response to neomycin. The authors noted that this sensitization rate is much lower than that seen when adults with chronic dermatoses are patch tested with neomycin. The authors stated that because topical antibiotics are mainly used on minor cuts and wounds, which are more common in children, the periodic use of topical antibiotics is unlikely to pose a sensitization problem. They also noted tht when sensitization to neomycin did occur, the reactions were mild and self-limiting.

Prystowsky et al. (Ref. 2) reported that in a general population of 1,158 subjects who were patch tested with 20 percent neomycin sulfate, 12 subjects (1.1 percent) showed sensitivity to neomycin. Ten of these 12 subjects had used neomycin for 1 week or longer on an inflammatory dermatosis. Use tests, in which commercial products containing neomycin 0.5 percent were applied three times a day for 7 days, were then conducted on these subjects. Three of the 12 subjects with positive patch tests had negative use tests. The authors concluded that these persons could possibly use neomycin-containing products for several days on minor cuts, wounds, and abrasions without experiencing persistent dermatitis. In patients who had positive reactions to the use test, the reactions were mild, self-limiting dermatoses. Prystowsky et al. concluded that the use of neomycin-containing products presents little risk

to the user. However, they emphasized that labeling should limit the use of such products to not more than 7 days because using these products for more than a week increases the chance of an allergic reaction.

The agency is aware of a study in which the estimated prevalence of positive neomycin patch test results was 0 percent in 50 "normal" subjects (Ref. 3). In another study the prevalence of positive neomycin patch tests was 3 percent in 100 "normal" subjects (Ref. 4). The agency is also aware that the rate of contact sensitivity to neomycin in patch test studies of dermatologic clinic populations was reported to be between 5 and 6 percent (Refs. 5, 6, and 7).

The data discussed above are sufficient to show that the general population is at a much lower risk of developing sensitization than persons who have chronic dermatitis or who have used neomycin-containing products for extended periods of time. Children, because of their play activities, are more likely than adults to have minor skin injuries and would be the more frequent users of topical antibiotics. However, among persons with chronic dermatitis, neomycin sensitization appears to be much less prevalent in children than in adults. Even when sensitization does occur, the symptoms are not severe and are localized and self-limiting. Also, the labeling on products containing neomycin includes warnings not to use the product for longer than 1 week and to discontinue use and consult a doctor if the condition persists or gets worse. For these reasons, the agency believes that concerns regading sensitization should not prevent placing neomycin in Category I as a first aid antibiotic.

References

(1) Leyden, J. J., and A. M. Kligman, "Contact Dermatitis to Neomycin Sulfate," *Journal of the American Medical Association*, 242:1276–1278, 1979.

(2) Prystowsky, S. D., et al., "Allergic Hypersensitivity to Neomycin," *Archives of Dermatology*, 115:713–715, 1979.

(3) Schorr, W. F., F. J. Wenzel, and S. I. Hegedus, "Cross-sensitivity and Aminoglycoside Antibiotics," *Archives of Dermatology*, 107:533–539, 1973.

(4) Patrick, J., J. D. Panzer, and V. J. Derbes, "Neomycin Sensitivity in the Normal (Nonatopic) Individual," *Archives of Dermatology*, 102:532–535, 1970.

(5) Fisher, A. A., "Contact Dermatitis," 2d Ed., Lea and Febiger, Philadelphia, 1973.

(6) Rudner, E. J., et al., "Epidemiology of Contact Dermatitis in North America: 1972," *Archives of Dermatology*, 108:537–540, 1973.

(7) Bandmann, H. J., et al., "Dermatitis From Applied Medicament," *Archives of Dermatology*, 106:335–337, 1972.

28. One comment contended that neomycin can sensitize the skin to agents such as the sun and cosmetics. A reply comment disagreed with the statement that neomycin can cause sensitivity to the sun and cosmetics and pointed out that allergens sensitize only to themselves or very closely related chemical entities.

The agency acknowleges that a variety of drugs can, theoretically, be altered by sunlight to form allergenic or irritating compounds, and that some drugs may interact with cosmetics to produce sensitivity. However, the comment submitted no data to show that neomycin caused such reactions, and a search of the literature revealed no information that neomycin is altered in this way.

G. Comments on Combinations and Dosage Forms

29. One comment requested that the proposed monograph be amended to provide for combinations of Category I antibiotics with Category I corticosteroids or Category I anesthetics. The comment contended that the Panel recognized the rationality of combining antibiotics with corticosteroids (42 FR 17671). The comment further stated that the Panel's concern that anesthetics in combination with antibiotics would mask signs of worsening infection was applicable only to products that were used to treat an existing infection. These concerns, the comment added, are not applicable to products that by definition are excluded from making anti-infective claims. The comment pointed out that the Topical Analgesic Panel approved a number of topical anesthetics for use on minor cuts and burns (42 FR 69864), and because the "combined attributes of such ingredients are indicated for simultaneous use in first aid type products," it would be inappropriate and against the public interest for FDA to ban topical antibiotic-anesthetic combinations.

Although the Panel stated that "it is entirely conceivable" to combine "certain" nonantibiotic ingredients, such as Category I corticosteroids, with antibiotics for reducing inflammation, the Panel believed that any such combination would have to be "properly evaluated." (See 42 FR 17671.) The agency points out that when the Topical Analgesic Panel evaluated corticosteroids in its report on OTC External Analgesic Drug Products (44 FR 69768), it considered hydrocortisone to be Category I as a topical analgesic, but only for use in single active ingredient drug products and not for use in combination drug products (44 FR 69787 and 69813).

Furthermore, the agency points out that no data on any antibiotic-nonantibiotic combination were submitted to the Antimicrobial II Panel for review, nor were any submitted in the comments. Although it may be "conceivable" that antibiotic and "certain" nonantibiotic ingredients could provide rational therapy for OTC use, this possibility is theoretical at present. In view of the Panel's concern that combinations of antibiotics with anesthetic ingredients could pose safety problems by masking signs of infection (42 FR 17672), the agency concludes that more information is needed to show that the population who would use antibiotic-nonantibiotic combinations on skin wounds would not be at risk. Until information is submitted to show that antibiotic-nonantibiotic combinations meet the criteria in 21 CFR 330.10(a)(4)(iv), such combinations will not be included in the monograph.

30. One comment objected to the Panel's restriction in § 342.10 (a), (b), and (c) of the dosage form of topical antibiotics to "topical ointment dosages" only. The comment stated that the term "ointment" is vague and unnecessarily restrictive. Referring to the definitions of cream and ointment in the United States Pharmacopeia (Ref. 1), the comment stated that "apparently one cannot readily distinguish ointments from creams since both dosage forms can be either water-in-oil or oil-in-water emulsions." The comment added that the Panel intended to include more than one dosage form in the monograph. To support this opinion, the comment cited several statements in the Panel's report, such as "ointment or any other topical dosage form" (42 FR 17675); and "ointment, powder or any other topical dosage form" (42 FR 17678). The comment requested that the term "ointment" be replaced in the monograph by the term "semi-solid dosage form," which would provide for more flexibility in the formulation of these products.

Several comments supported the recommended restriction to the ointment dosage form only. One comment theorized that a petrolatum (ointment) base may actually be more effective than a cream base because the occlusive effect of the ointment allows transepidermal moisture to solubilize the antibiotic, producing a higher concentration of the drug at the site of action than the concentration that would be delivered by a cream at the same labeled potency. Another comment argued that ointment bases are

preferable because they rarely produce allergic sensitization; whereas creams, which contain potential allergens, such as preservatives, emulsifiers, antioxidants, lanolin, wood alcohols, and perfumes, often produce allergic sensitization. Another comment stated that these added ingredients could delay wound healing.

The agency points out that manufacturers of OTC topical antibiotics must comply not only with the OTC drug regulations, but also with the antibiotic drug regulations in Subparts F of Parts 444, 446, and 448 (21 CFR Parts 444, 446, and 448), which establish standards of identity, strength, quality, and purity. In the **Federal Register** of October 28, 1980 (45 FR 71354), FDA published a final rule amending the antibiotic drug regulations (21 CFR 433.1) to exempt dermatologic antibiotic drug products, including those subject to the OTC drug review, from batch certification. The agency recognizes that the acceptable dosage forms for the various topical antibiotics are characterized in the antibiotic monographs and therefore sees no need to specify particular dosage forms in this OTC drug monograph. Manufacturers are restricted to using only those dosage forms that are contained in the antibiotic regulations.

The agency agrees that the traditional cream bases have been shown to produce allergic sensitization more often than petrolatum-type ointment bases, but recognizes that creams can be formulated to omit many of the potential allergens. Almost any preparation can produce an allergic reaction in some individuals. However, such reactions are usually not severe, and the agency believes that the labeling of topical antibiotic drug products adequately warns the user to consult a doctor if the condition worsens. Because no data were presented to support the contentions that ointments are more effective or that ingredients in cream preparations delay wound healing, these comments are not being adopted.

Reference

(1) "The United States Pharmacopeia," 19th Rev., United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 700–702, 1975.

II. The Agency's Tentative Adoption of the Panel's Report

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

1. *Summary of ingredient categories.* The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and has proposed the recategorization of neomycin sulfate from Category III to Category I as well as a change in the designation of the drug product categories from skin wound antibiotic and skin wound protectant to topical first aid antibiotic. For the convenience of the reader, the following table is included as a summary of the categorization of topical antibiotic ingredients by the agency.

First aid antibiotic active ingredients	Category
Bacitracin	I.
Bacitracin zinc	I.
Chlortetracycline hydrochloride	I.
Gramicidin	III.
Neomycin sulfate	I.
Oxytetracycline hydrochloride	I.
Polymyxin B sulfate (in combination only)	I.
Tetracycline hydrochloride	I.

2. *Testing of Category II and Category III conditions.* The Panel recommended testing guidelines for topical antibiotic drug products (42 FR 17678). The agency is offering these guidelines as the Panel's recommendations without adopting them or making any formal comment on them except as otherwise noted in this document. (See comments 16 and 18 above.) Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any antibiotic drug product ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the **Federal Register** of September 29, 1981 (46 FR 47740). This policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Changes in the Panel's Recommendations

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the Panel's report and recommended monograph with the changes described in FDA's response to the comments above and with other changes described in the summary below. A summary of the changes made in the Panel's recommendations and conclusions follows.

1. Part 342—Topical Antibiotic Drug Products For OTC Human Use has been renumbered as follows: Part 333—Topical Antimicrobial Drug Products For OTC Human Use, Subpart B—Topical First Aid Antibiotic Drug Products. (See Supplementary Information above.)

2. The two topical antibiotic drug product categories, skin wound protectant and skin wound antibiotic, have been combined and renamed "first aid antibiotic." The definition for first aid antibiotic is "an antibiotic-containing drug product applied topically to the skin to help prevent infection in minor cuts, scrapes, and burns." (See comment 5 above.)

3. The required indication for the first aid antibiotic drug product category is: "First aid to help prevent infection in minor cuts, scrapes, and burns." Certain allowable phrases may be used in addition to this indication. (See proposed § 333.150(b) (2) and (3).) Protectant claims have been deferred to the rulemaking for skin protectant drug products. (See comment 5 above.)

The indication "treats infection" is in Category II because it is not suitable for OTC first aid antibiotic labeling. (See comment 13 above.)

4. The agency has included bacitracin zinc in addition to bacitracin as a Category I first aid antibiotic ingredient in this tentative final monograph. Both bacitracin and bacitracin zinc were included in products submitted to the OTC drug review. Although both ingredients were discussed in the Panel's report, bacitracin zinc was inadvertently omitted from the Panel's recommended monograph. The agency has corrected this oversight by including bacitracin zinc in this tentative final monograph.

5. The Panel's recommended monograph stated the concentration of antibiotic ingredients as "not less than *x* amount per gram," but did not specify an upper limit. The agency has clarified these ingredient concentrations by stating the labeled amounts of each antibiotic consistent with the requirements of the applicable antibiotic drug monographs (Subparts F of Parts 444, 446, and 448). Bacitracin concentration has been restated from not less than 500 units per gram (units/g) to 500 units/g. The concentration for all three of the tetracyclines has been set at 30 milligrams per gram (mg/g). The Panel's recommended monograph set oxytetracycline hydrochloride at not less than 30 mg/g, tetracycline hydrochloride at not less than 15 mg/g, and chlortetracycline hydrochloride at not less than 1 mg/g. The agency notes that various products containing the three tetracyclines reviewed by the Panel all contained 30 mg/g. Polymyxin B sulfate concentration has been revised to between 5,000 to 10,000 units/g instead of 4,000 to 5,000 units/g as recommended by the Panel. The agency notes that various polymyxin

combination products reviewed by the Panel contained polymyxin 5,000, 8,000, and 10,000 units/g. The Panel recommended a neomycin sulfate concentration of not less than 5 mg/g of finished ointment dosage form. This could be interpreted as requiring a specific 5-mg weight of neomycin sulfate to be contained in each gram of suitable vehicle. Because the antibiotic activity in a milligram of neomycin sulfate can vary depending on the purity of the material, it is better to designate the neomycin content on an activity basis. (See 21 CFR 430.6(b)(20).) Therefore, the neomycin sulfate concentration has been revised to an amount of neomycin sulfate equivalent to the antibiotic activity of 3.5 mg neomycin per gram of vehicle. (See 21 CFR 444.542a(a).)

6. Neomycin sulfate was listed in Category III in the Panel's report because of safety concerns about the potential of this ingredient to cause sensitization or antibiotic-resistant staphylococci. Neomycin sulfate has been classified as a Category I first aid antibiotic in this tentative final monograph. (See comments 24 through 28 above.)

7. In its recommended monograph, the Panel specifically listed acceptable combinations if they met the Panel's criteria for combinations and if a monograph existed for the combination in the antibiotic drug regulations. Similarly, the monograph provided only for those dermatologic dosage forms that were contained in the antibiotic drug regulations for OTC topical antibiotics.

The tentative final monograph has been revised to state that OTC topical antibiotic drug products must conform not only to the OTC drug regulations, but also to the antibiotic drug regulations (Subpart F of Parts 444, 446, and 448), thus obviating reference to specific antibiotic monographs.

The Panel concluded that to qualify as a Category I combination product, each of the following conditions must be met:

a. Each active antibiotic and claim in the combination product is Category I.

b. The active antibiotic ingredients are combined on the basis of broadening the relevant antimicrobial spectrum.

c. The total number of ingredients does not exceed three.

The agency concurs with the Panel's criteria for combinations and has proposed in the tentative final monograph a combination policy consistent with these criteria as follows:

The Category I antibiotic active ingredients are grouped according to antibacterial activity.

Group A. *Broad-spectrum antibiotics:*
Chlortetracycline hydrochloride
Neomycin sulfate
Oxytetracycline hydrochloride
Tetracycline hydrochloride

Group B. *Antibiotics with primarily gram-positive activity:*
Bacitracin
Bacitracin zinc

Group C. *Antibiotic with primarily gram-negative activity:*
Polymyxin B sulfate

First aid antibiotic drug products may contain a single antibiotic ingredient chosen from either Group A or Group B. Antibiotic ingredients in Group C must be used in combination with at least one other antibiotic from Group A or B. Any combination of up to three antibiotic ingredients may be marketed provided only one antibiotic is chosen from each group.

The agency points out that, because OTC first aid antibiotics are subject to both an OTC final monograph and the antibiotic drug regulations, only those combinations for which an antibiotic certification monograph exists in Subparts F of Parts 444, 446, and 448 may be legally marketed.

8. The agency has combined and revised the warnings in § 342.50(b)(1), (4), and (5) and § 342.52(b)(1), (4), and (5) for clarity and to eliminate duplicative words. The agency has also added "animal bites" to the revised warnings, which appear in § 333.150(c)(1) in this tentative final monograph as follows: "For external use only. Do not use in the eyes or apply over large areas of the body. In case of deep or puncture wounds, animal bites, or serious burns, consult a doctor."

9. The agency has revised the Panel's recommended directions for use in § 342.50(c) and § 342.52(c) to make them clearer and simpler. This information appears in § 333.150(d) in this tentative final monograph as follows: "Clean the affected area. Apply a small amount of this product one to three times daily. May be covered with a sterile bandage."

To eliminate inconsistencies and duplication, the warning and caution statements for OTC topical antibiotic-containing drugs included in 21 CFR 369.20 and 369.21 will be revoked when the final monograph becomes effective.

10. In several of its warnings, the Panel recommended the phrase, "see a physician," which has often been used in OTC drug labeling as advice to the consumer in case of symptoms that indicate a condition that cannot be self-treated. Believing that the word "doctor" is more commonly used and better understood by consumers, the agency proposes to substitute "doctor" for "physician" in the warnings appearing in the tentative final monograph. This change is part of a continuing effort to achieve OTC drug labeling language that is simple, clear, and accurate, in keeping with § 330.10(a)(4)(v), which states in part, "Labeling * * * shall state the intended uses and results of the product; adequate directions for proper use; and warnings against unsafe use, side effects, and adverse reactions in such terms as to render them likely to be read and understood by the ordinary individual, including individuals of low comprehension, under customary conditions of purchase and use." If the word "doctor" is adopted in the final monograph, the agency will use this language in other final monographs and other applicable OTC drug regulations and will propose amendments to those regulations accordingly. Public comment on this proposed change in labeling language is invited.

The agency has examined the economic consequences of this proposed rulemaking and has determined that it does not require either a Regulatory Impact Analysis, as specified in Executive Order 12291, or a Regulatory Flexibility Analysis, as defined in the Regulatory Flexibility Act (Pub. L. 96-354). Specifically, the proposal would necessitate some relabeling, resulting in minimal costs. Manufacturers may wish to test the one ingredient that is in Category III, but testing costs would be voluntary because products containing this ingredient may also be reformulated. Costs associated with reformulation include stability testing. Therefore, the agency concludes that the proposed rule is not a major rule as defined in Executive Order 12291. Further, the agency certifies that the proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC topical first aid antibiotic drug products. Types of impact may include, but are not limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC topical first aid antibiotic drug products should be accompanied by appropriate documentation. Because the agency has not previously invited specific comment on the economic impact of the OTC drug review on topical first aid antibiotic drug products, a period of 120 days from the date of publication of this proposed rulemaking in the **Federal Register** will be provided for comments on this subject to be developed and transmitted.

The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

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

List of Subjects in 21 CFR Part 333

OTC drugs: Topical antibiotics.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 as revised (see 47 FR 16010; April 14, 1982) it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended in proposed Part 333 by adding new Subpart B, to read as follows:

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

Subpart B—Topical First Aid Antibiotic Drug Products

Sec.

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704).

§ 333.101 Scope.

(a) An over-the-counter first aid antibiotic 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, each of the general conditions established in § 330.1, the exemptions established in § 433.1, and the applicable sections of Subpart F of Parts 444, 446, and 448.

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

§ 333.103 Definitions.

As used in this subpart:

(a) *Antibiotic drug.* In accordance with section 507(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 357(a)), "any drug intended for use by man containing any quantity of any chemical substance which is produced by a microorganism and which has the capacity to inhibit or destroy microorganisms in dilute solution (including the chemically synthesized equivalent of any such substance)."

(b) *First aid antibiotic.* An antibiotic-containing drug product applied topically to the skin to help prevent infection in minor cuts, scrapes, and burns.

§ 333.110 First aid antibiotic active ingredients.

The active ingredient of the product consists of any of the following within the specified concentration established for each ingredient:

(a) *Broad-spectrum anitbiotics.* (1) Chlortetracycline hydrochloride 30 milligrams per gram.

(2) Neomycin sulfate equivalent to the antibiotic activity of 3.5 milligrams neomycin per gram.

(3) Oxytetracycline hydrochloride 30 milligrams per gram.

(4) Tetracycline hydrochloride 30 milligrams per gram.

(b) *Antibiotics with primarily gram-positive activity.*

(1) Bacitracin 500 units per gram.

(2) Bacitracin zinc 500 units per gram.

(c) *Antibiotic with primarily gram-negative activity.* Polymyxin B sulfate 5,000 to 10,000 units per gram for use only in combination as provided in § 333.120.

§ 333.120 Permitted combinations of active ingredients.

Two or three ingredients identified in § 333.110 may be combined provided the combination contains only one ingredient from each class of antibiotics identified in § 333.110(a), (b), and (c), and provided the combination meets the conditions in § 433.1 and in the applicable sections of Subparts F of Parts 444, 446, and 448.

§ 333.150 Labeling of first aid antibiotic drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "first aid antibiotic."

(b) *Indications.* (1) The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the phrase, "First aid to help prevent infection in minor cuts, scrapes, and burns."

(2) *Other allowable indications.* In addition to the required indication identified in § 333.150(b)(1), the labeling of the product may contain additional indications under the heading "Indications" that are limited to any of the following phrases:

(i) (Select one of the following: "Decreases" or "Helps reduce") "the number of bacteria on the treated area."

(ii) "Helps" (select one of the following: "prevent," "guard against," or "protect against") "skin infection."

(iii) "Helps reduce the" (select one of the following: "risk" or "chance") "of skin infection."

(iv) "Helps prevent bacterial contamination in minor cuts, scrapes, and burns."

(3) *Other allowable statements.* In addition to the required information specified in § 333.150(a), (b)(1), (c), and (d), the labeling of the product may contain any of the following statements, provided such statements are neither placed in direct conjunction with information required to appear in the labeling nor occupy labeling space with greater prominence of conspicuousness than the required information.

(i) "First aid product."

(ii) "Antibiotic medication for minor cuts, scrapes, and burns."

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

(1) "For external use only. Do not use in the eyes or apply over large areas of the body. In case of deep or puncture wounds, animal bites, or serious burns, consult a doctor."

(2) "Stop use and consult a doctor if the condition persists or gets worse. Do not use longer than 1 week unless directed by a doctor."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions": "Clean the affected area. Apply a small amount of this product one to three times daily. May be covered with a sterile bandage."

Interested persons may, on or before September 17, 1982 submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on

the agency's economic impact determination may be submitted on or before November 8, 1982. 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 above office 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 July 11, 1983 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 September 9, 1983. 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 above office between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on September 9, 1983. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register** unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Dated: April 16, 1982.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Dated: June 7, 1982.

Richard S. Schweiker,

Secretary of Health and Human Services.

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