DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 333 and 369

[Docket No. 76N-0482]

Topical Antimicrobial Drug Products for Over-the-counter Human Use; Final Monograph for OTC First Aid Antibiotic Drug Products

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing 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 final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and all new data and information on topical first aid antibiotic drug products that have come to the agency's attention. This final monograph is part of the ongoing review of OTC drug products conducted by FDA.

DATE: December 12, 1988.

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

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 (21 CFR Part 342), 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 accordance with § 330.10(a)(10), the data and information considered by the Panel were put on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, after deletion of a small amount of trade secret information.

The agency's proposed rule, in the form of a tentative final monograph, for OTC first aid antibiotic drug products was published in the **Federal Register** of July 9, 1982 (47 FR 29986). FDA proposed to add a new Subpart B to Part 333 rather than continue the rulemaking under Part 342 as designated in the advance notice of proposed rulemaking for OTC topical antibiotic drug products. The redesignation of parts is discussed further in the tentative final monograph at 47 FR 29986. Interested persons were invited to file by September 7, 1982, written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal. Interested persons were invited to file comments on the agency's economic impact determination by November 8, 1982. New data could have been submitted until July 11, 1983, and comments on the new data until September 9, 1983. Final agency action occurs with the publication of this final monograph, which is a final rule establishing a monograph for OTC first aid antibiotic drug products.

The OTC procedural regulations (21 CFR 330.10) now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA is no longer using the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but is using instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III).

As discussed in the proposed regulation for OTC topical first aid antibiotic drug products (47 FR 29986), the agency advises that the conditions under which the drug products that are subject to this monograph will be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication in the **Federal Register**. Therefore, on or after December 12, 1988, no OTC drug products that are subject to the monogrpah 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 application. Further, any OTC drug product subject to this monograph that is repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date and, as soon as they comply, a Form 6 (Form FD 356H, formerly Form FD 1675) will no longer be required. (See comment 2 below.)

In response to the proposed rule on OTC topical first aid antibiotic drug products, a bi-state drug information center, a drug manufacturers' association, and three drug manufacturers submitted comments. Copies of the comments and data received are on public display in the Dockets Management Branch. Any additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch.

In proceeding with this final monograph, the agency has considered all objections and the changes in the procedural regulations.

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 notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

I. The Agency's Conclusions on the Comments

A. General Comments on OTC First Aid Antibiotic Drug Products

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

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products, published in the **Federal Register** of May 11, 1972 (37 FR 9464); in paragraph 3 of

the preamble to the tentative final monograph for OTC antacid drug products, published in the **Federal Register** of November 12, 1973 (38 FR 31260); and in paragraph 1 of the preamble to the tentative final monograph in the present proceeding (47 FR 29987). FDA reaffirms the conclusions stated in those documents. Court decisions have confirmed the agency's authority to issue substantive regulations by rulemaking. See, e.g., *National Nutritional Foods Association* v. *Weinberger*, 512 F.2d 688, 696–98 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers* v. *FDA*, 487 F. Supp. 412 (S.D.N.Y 1980), *aff'd* 637 F.2d 887 (2d Cir. 1981).

2. One comment stated that antibiotic dosage forms that would appear in 21 CFR Part 333 would be, by definition, generally recognized as safe and effective, and that agency approval of a Form 6 should not be required before marketing. The comment pointed out that this approach would be consistent with the requirements for all other OTC drug products that are subjects of OTC drug monographs and that were previously considered new drugs. Therefore, the comment requested that the requirement for a Form 6 be deleted for any antibiotic drug product that is subject to the final monograph on OTC first aid antibiotic drug products. The comment added that if Form 6 requirements are to be retained, then the effective date of the final monograph should be 24 months, rather than 12 months, after publication of the final rule. The comment pointed out that, although 12 months would be reasonable for most other drug products included in the OTC drug review, the Form 6 requirement for antibiotic drug products makes them a special case because FDA preapproval of the Form 6 submissions for manufacturing, control, and labeling changes is a time-consuming process.

The agency agrees that approval of an abbreviated antibiotic application (formerly a Form 6) is not a prerequisite to marketing an antibiotic drug product that meets the requirements of this final monograph. OTC drug products that meet the conditions established in Part 330 and the applicable monograph are generally recognized as safe and effective and not misbranded and may be marketed without an approved application or abbreviated application.

The agency recently revised 21 CFR 433.1 to make clear that an antibiotic drug that meets the general requirements established in 21 CFR 330.1 and the requirements of a final OTC drug monograph is exempt from the batch certification requirements of section 507 of the Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 357) even without having an approved antibiotic application (formerly a Form 5) or an abbreviated antibiotic application. This clarification was proposed in the **Federal Register** of July 22, 1985 (50 FR 29702) and made final in the **Federal Register** of July 15, 1986 (51 FR 25523).

Because the final monograph does not become effective until 12 months after its publication, technically an abbreviated application would continue to be required for one year after publication of the final rule. The agency does not believe that this requirement is necessary for first aid antibiotic drug products that comply with the conditions of the final monograph. Therefore, manufacturers may market products that comply with the final monograph without an approved abbreviated application during this period, i.e., between December 11, 1987, and December 12, 1988. Manufacturers currently marketing these products under an approved abbreviated application should notify FDA when the product is being marketed under the final monograph, so that the applicability of the abbreviated application can cease. Eventually, FDA will revoke all applications and abbreviated applications that are in effect for products covered by the final monograph.

The request that FDA give a later effective date to the monograph to allow time for Form 6 approvals is moot because an abbreviated application (Form 6) is not required if the first aid antibiotic product meets the conditions of the final monograph.

3. One comment requested that conflicts between the tentative final monograph for OTC topical antibiotic drug products and the existing antibiotic regulations be resolved by incorporating appropriate sections of the existing antibiotic regulations in Subparts F of Parts 444, 446, and 448 into the OTC first aid antibiotic monograph and by deleting those portions that are so incorporated from the antibiotic regulations. The comment contended that this action would eliminate the confusion caused by conflicting requirements for a single product as well as distinguish clearly between antibiotic products that are generally recognized as safe and effective for OTC use and those that are still subject to prescription dispensing and premarketing approval. The comment stated that if necessary, to ensure a safe and effective product, the detailed standards and testing requirements found in the antibiotic regulations may be retained in the OTC drug monograph.

The agency agrees that appropriate portions of the regulations on dermatologic dosage forms in Parts 444, 446, and 448 should be incorporated into the final monograph for OTC first aid antibiotic drug products. The agency consequently is revising the format proposed in the tentative final monograph. The agency is not grouping and combining antibiotic ingredients on the basis of antibacterial activity, and including a cross-reference to Subpart F of Parts 444, 446, and 448. In this final monograph, FDA is including a complete listing of the antibiotic active ingredients (§ 333.110) and the combinations of those ingredients (§ 333.120) that are generally recognized as safe and effective, as well as the concentrations permitted for each of those ingredients and the appropriate dosage forms for the products. The dosage forms included in the monograph reflect those dosage forms currently identified in Subpart F of the specific antibiotic regulations (Parts 444, 446, and 448) that apply to OTC first aid antibiotics. There is an established testing methodology, derived from approved antibiotic applications, for these first aid antibiotic ingredients and combinations in the antibiotic regulations. The final monograph also includes references to the appropriate tests and methods of assay that are set forth in the existing antibiotic regulations and that are applicable to particular antibiotic ingredients and combinations.

All drug products included in the final monograph for OTC first aid antibiotic drug products are generally recognized as safe and effective and not misbranded. Therefore, they do not need premarket approval and are exempt from batch certification requirements. For both marketing control and agency regulatory purposes, it is necessary that appropriate standards and methodology i.e., tests and methods of assay, be established before a first aid antibiotic drug product can be considered generally recognized as safe and effective for OTC use. Any firm interested in marketing a single monograph ingredient in a dosage form not included in the monograph, or a combination of monograph ingredients not currently included in the monograph, may submit an antibiotic application to FDA for review and evaluation or file a petition (with appropriate supporting data, including proposed standards and methodology) to amend the monograph.

4. One comment disagreed with the agency's tentative decision to transfer products and claims for skin wound protectants that do not contain antimicrobial active ingredients to the rulemaking for OTC skin protectant drug products. The comment argued that, although a skin wound protectant may not contain an antimicrobial ingredient, the indications for use of the product (protect wounds against microbial contamination) place it more appropriately in the rulemaking for OTC topical antimicrobial drug products than in the rulemaking for OTC skin protectant drug products. The comment contended that skin protectants are generally used on intact skin and do not serve the same function as skin *wound* protectants, which are indicated for prevention of wound contamination by providing a physical barrier to the entry of dirt and bacteria. The comment added that if the absence of active [antimicrobial] ingredients prohibits the inclusion of skin wound protectants in the monograph for OTC antimicrobial drug products, then there is justification for classifying skin wound protectants that act only as a physical barrier to contamination as medical devices because skin wound protectants "act simply as a physical barrier to contamination and do not affect the structure or function of the body or exert a microbiocidal effect."

The agency believes that the concerns raised by the comment are rendered moot by FDA's decision not to adopt the Panel's recommendation for separate categories of "skin wound protectants" and "skin wound antibiotics." This rulemaking is intended to address only OTC topical drug products that contain antibiotics. Therefore, as FDA explained in the tentative final rule, only one category is necessary for this rulemaking—"first aid antibiotics."

FDA is placing all products that are considered as "skin wound protectants" and that do not contain an antibiotic in the skin protectant rulemaking for consideration of the skin wound protectant claims. The tentative final monograph for OTC skin protectant drug products, published in the **Federal Register** of February 15, 1983 (48 FR 6820), includes in proposed § 347.50(b)(1) the indication "For the temporary protection of minor cuts, scrapes, burns, and sunburn." This skin protectant category, which is similar to the skin wound protectant indication recommended by the Antimicrobial II Panel (42 FR 17680), covers the type of product described in the comment.

Because this final monograph applies only to products containing an antibiotic, the agency is not considering in this document the issue of whether skin wound protectants that do not contain antimicrobials should be subject to the skin protectant rulemaking or be considered a medical device. That issue will be discussed in the rulemaking for OTC skin protectant drug products.

B. Comments on Labeling of OTC First Aid Antibiotic Drug Products

5. One comment contended that FDA does not have the statutory authority to prescribe exclusive list of terms from which indications for use of OTC drug products must be drawn and to prohibit labeling terminology which is truthful, accurate, not misleading, and intelligible to the consumer. The comment also expressed its intention to make a more detailed statement on the exclusivity policy at the September 29, 1982 hearing on this issue.

In the **Federal Register** of May 1, 1986 (51 FR 16258), the agency published a final rule changing its labeling policy for stating the indications for use of OTC drug products. Under the final rule, the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either (1) the specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "APPROVED USES"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "APPROVED USES"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "APPROVED USES," plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All required OTC drug labeling other than indications for use (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under an OTC drug monograph where exact language has been established and identified by quotation marks in an applicable monograph or other regulation, e.g., 21 CFR 201.63 or 330.1(g).

In the tentative final monograph (47 FR 29999), supplemental language relating to indications had been proposed and captioned as *Other Allowable Indications* and *Other Allowable Statements*. Under FDA's revised labeling policy (51 FR 16258), such statements are included at the tentative final stage as examples of other truthful and nonmisleading language that would be allowed elsewhere in the labeling. In accordance with the revised labeling policy, such statements would not be included in a final monograph. However, the agency has decided that, because these additional terms have been reviewed by FDA, they should be incorporated, wherever possible, in final OTC drug monographs under the heading "Indications" as part of the indications developed under that monograph. (See part III. paragraph 3. below—SUMMARY OF SIGNIFICANT CHANGES FROM THE PROPOSED RULE.)

6. One comment disagreed with the agency's proposed substitution of the word "doctor" for "physician" in OTC drug labeling. The comment stated that because "physician" is a term that is recognized by people of all ages and social and economic levels, there is no need for the change, which would be costly and provide no benefit. The comment further contended that "physician" is a more accurate term, whereas "doctor" is a broad term that could confuse and mislead the lay person into taking advice on medication from persons other than medical doctors, such as optometrists, podiatrists, and even chiropractors. Another comment favored the use of common, simple, and easily understood language in labeling. This comment noted that both "doctor" and "physician" are equally accurate and meaningful and argued that neither term should be prohibited, but instead flexibility to use either term should be allowed.

In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs, including the one for OTC first aid antibiotic drug products, to substitute the word "doctor" for "physician" in OTC drug monographs on the basis that the word "doctor" is more commonly used and better understood by consumers. Based on comments received to these proposals, the agency has determined that final monographs and any applicable OTC drug regulation will give manufacturers the option of using either the word "physician" or the word "doctor." This final monograph provides that option (see § 333.150(e)).

7. Noting that the Panel defined an antibiotic as an agent that either destroys susceptible bacteria or arrests their development, one comment disagreed with the agency's proposed Category II classification of the claim "Helps kill bacteria." The comment contended that this claim is accurate "in that an antibiotic is capable of either killing bacteria or affecting them so that

they can be eliminated more easily by the body's natural defenses." The comment argued that this claim has been used for decades with no known harm to the consumer due to product misuse and that, because first aid antibiotics are not indicated for treatment of infection, the potential for harm due to misuse is also reduced. According to the comment, the agency's concern is theoretical and not substantiated. The comment requested that the agency allow the phrase "helps kill bacteria" as a Category I claim for OTC first aid antibiotics.

In the tentative final monograph, the agency noted that "according to the definition in section 507(a) of the act (21 U.S.C. 357(a)), antibiotics have the capacity to inhibit or destroy microorganisms." (See comment 12, 47 FR 29991.) However, the agency expressed its belief 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." The agency still believes that the claim "helps kill bacteria" could be potentially misleading to the average consumer if directly associated with the term "infection" that is included in the indication. However, the agency acknowledges that this information is familiar to the average consumer and may be useful in describing the product's action or intended effect. Therefore, the agency would allow the claim to be included in labeling provided it is not intermixed with monograph labeling.

The OTC drug review program establishes conditions under which OTC drugs are generally recognized as safe and effective and not misbranded. One aspect of the program is to develop standards for certain parts of the labeling of OTC drug products. FDA has found that it is simply not practical—in terms of time, resources, and other considerations—to set standards for all labeling found on OTC drug products. Accordingly, OTC drug monographs directly address only those labeling items that are related in a significant way to the safe and effective use of covered products by lay persons. These labeling items are the product statement of identity; names of active ingredients; indications for use; directions for use; warnings against unsafe use, side effects, and adverse reactions; and claims concerning mechanism of drug action.

The agency finds that the claim "helps kill bacteria" requested by the comment, while descriptive of the action of first aid antibiotic drug products, does not relate in a significant way to the safe and effective use of these products and, therefore, is outside the scope of the monograph.

However, the OTC drug review is also intended to ensure that OTC drug products are not misbranded. Therefore, the agency evaluates claims made on OTC drug product labels on a product-by-product basis, under section 502 of the act (21 U.S.C. 352), to determine whether those claims are false or misleading. Any claim that is outside the scope of the monograph, even though it is truthful and not misleading, may not appear on any portion of the labeling that is required by the monograph. Such a claim also may not detract from the required information. Therefore, the claim requested by the comment may be included on the labeling of OTC first aid antibiotic drug product provided that it is not intermixed with labeling established by the monograph, and that it is not false or misleading.

C. Comments on Gramicidin

8. One comment objected to the Category III classification of gramicidin for safety, stating that the Antimicrobial II Panel apparently decided that gramicidin should be placed in Category III because it "is a potent hemolytic agent." The comment contended that the data supporting this conclusion appear to be quite sparse and are probably a carry-over from the remote observation by Heilman and Herrell (Ref. 1) in 1941 that tyrothricin, a crude preparation containing tyrocidine and gramicidin, had in vitro hemolytic properties against rabbits' and sheep's erythrocytes. The comment cited the animal study by Robinson and Molitor (Ref. 2) as indicating that relatively large intravenous or intraperitoneal doses of gramicidin suspensions were needed to show toxicity. The comment contended that the doses used in this study should be compared with a daily topical human dosage of 0.0083 milligram per kilogram (mg/kg) (0.25 mg gramicidin per gram (g) of ointment, assuming application of 2 g ointment per day to a 60-kg subject). The comment also cited a report (Ref. 3) in which it was noted that an unpublished study by Leyden reports that gramicidin was not detected in the serum or urine of eight subjects with widespread atopic dermatitis or psoriasis who were treated twice daily for 7 days with 30 g of a cream containing (among other antibiotics) gramicidin 0.25 milligram per gram (mg/g).

The comment further noted that the safety and efficacy of gramicidin have been fully discussed in data submitted to FDA (as part of the drug efficacy study implementation (DESI) program) concerning a certified prescription topical product containing gramicidin, neomycin sulfate, nystatin, and triamcinolone acetonide. The comment concluded that the extensive use of gramicidin for over 20 years in both OTC and prescription topical preparations has not resulted in any reports of adverse effects related to any possibility of gramicidin toxicity.

After reevaluating the information on the safety of gramicidin and considering the data cited by the comment, the agency concludes that gramicidin is not generally recognized as safe for OTC use as a first aid antibiotic. The Panel recommended that the safety of gramicidin be studied to determine both systemic and topical toxicity. The Panel said specifically that the amount of gramicidin absorbed through the skin following topical application and the hemolytic (red blood cell breakdown) potential of gramicidin resulting from absorption through fresh superficial wounds need to be determined (42 FR 17660). This information has not been provided.

The agency disagrees with the comment that evidence of hemolytic activity of gramicidin is sparse and notes that reports of such activity were published after the report cited by the comment (Ref. 1). Although, as the comment stated, Heilman and Herrell (Ref. 1) first reported that crude tyrothricin was hemolytic, they later reported that purified gramicidin was also hemolytic (Ref. 4). Dubos and Hotchkiss (Ref. 5) and Rammelkamp and Weinstein (Refs. 6 and 7) concluded that the hemolytic effect of tyrothricin was primarily the result of the tyrocidine content of tyrothricin, although they noted that gramicidin in high concentrations also exhibited hemolytic and leukocytolytic effects. There have also been some reports in which gramicidin was modified in an attempt to reduce the hemolytic activity (Ref. 8, 9, and 10). Lewis et al. (Ref. 8) found that treatment of gramicidin with formaldehyde lowered the hemolytic activity of gramicidin 80 to 90 percent without decreasing its antibacterial properties. Schales and Mann (Ref. 9), although noting that the hemolytic effect of gramicidin was considerably slower than that of tyrocidine, found that various gramicidin derivatives had hemolytic activity that varied from 2 to 87 percent of that of gramicidin. Rambhav and Ramachandran (Ref. 100) evaluated the hemolytic activity of gramicidin and several modified gramicidins and concluded that the

peptide-bound ethanolamine residue was implicated in the hemolytic activity of gramicidin.

Even though Robinson and Molitor (Ref. 2) reported that gramicidin was not toxic when given orally (at 1,000 mg/kg) or injected subcutaneously or intradermally, gramicidin was highly toxic upon parenteral administration. Acute parenteral dosages of 1.25 mg/kg gramicidin administered intravenously or 10 mg/kg administered intraperitoneally were not lethal in mice. The lethal dose for mice by the intravenous route was 3.75 mg/kg.

In most dogs, daily intravenous dosing of gramicidin at 2 mg/kg was lethal within 2 to 3 days. Robinson and Molitor noted that in the case of tyrothricin, daily blood examinations showed that all dogs receiving 2 to 4 mg/kg tyrothricin developed marked leucocytosis. Dogs tolerating more than 10 consecutive doses of the drug became anemic, the erythrocyte count ranging from 2.06×10^5 to 3.95×10^5 cells per cubic millimeter. One dog with marked leucocytosis and anemia returned to normal after 2 months during which no drug was given. Robinson and Molitor suggested that this finding might indicate that the anemia caused by daily injections of tyrothricin is related to the hemolytic properties, which it can display in vitro. The authors noted that gramicidin had no apparent effect upon the blood picture during the short period that the animal survived. They also suggested that equivalent doses of gramicidin might have a similar effect as tyrothricin if the animal could tolerate a larger number of consecutive doses.

Robinson and Molitor noted that the impossibility of preparing true aqueous solutions of gramicidin made it difficult to interpret the data, particularly the data from the intravenous test groups in which physical factors such as large particle size may influence the results. They suggested that in view of the insolubility of gramicidin, it is possible that the effects observed were not caused by a specific pharmacodynamic action but rather were caused by nonspecific physical or physicochemical properties. Robinson and Molitor concluded that it is doubtful whether the toxicological results they reported of parenteral use in animals would have a direct bearing on the clinical use of gramicidin topically, except that application to deep lacerated wounds might approach the experimental conditions present in intravenous injection. Therefore, they cautioned against use of gramicidin where rapid and direct absorption into the bloodstream is likely to occur. As noted above, the Panel was concerned about the hemolytic potental of gramicidin resulting from absorption through fresh superficial wounds. The agency concurs based on the above discussion.

As the comment noted, Leyden (Ref. 3) reported that no significant blood or urine levels could be detected in human subjects after very extensive topical application of a cream containing 0.25 mg/g gramicidin, neomycin sulfate, and polymyxin B sulfate to atopic dermatitis or psoriasis. However, only eight subjects were studied. A limited report of this type is not adequate to establish general recognition of the safety of this ingredient for OTC first aid use. The report does not indicate whether the drug was applied to intact or broken skin, does not describe the assay method, and does not state how many subjects were treated with the cream that contained gramicidin or how many were treated with an alternate ointment that did not contain gramicidin. The information provided seems, on the whole, rather limited especially when the no-effect toxic dose of gramicidin is unknown.

The comment also referred to a prescription product containing gramicidin in combination with other ingredients that is being evaluated under the agency's DESI program. As discussed in comment 9 below, the agency concluded in a DESI notice published in the **Federal Register** of April 17, 1985 (50 FR 15227) that the combination drug policy is satisfied with respect to nystatin and triamcinolone acetonide, two of the four ingredients in the prescription product, for the treatment of cutaneous candidiasis, and the company has agreed to reformulate the product to delete neomycin and gramicidin, the other two ingredients (Ref. 11).

The agency concludes that sufficient data have not been submitted on the absorption of gramicidin and on the hemolytic potential of gramicidin resulting from absorption through fresh superficial wounds. Accordingly, gramicidin is not being included in this final monograph.

References

(1) Heilman, D., and W.E. Herrell, "Hemolytic Effect of Gramicidin," *Proceedings of the Society for Experimental Biology and Medicine*, 46:182–184, 1941.

(2) Robinson, H.J., and H. Molitor, "Some Toxicological and Pharmacological Properties of Gramicidin, Tyrocidine, and Tyrothricin," *Journal of Pharmacology and Experimental Therapeutics*, 74:75–82, 1942.

(3) Bushby, S.R.M., "Blood Concentrations Following Topical Application," *in* "Over-the-Counter Topical Antibiotic Products: Data on Safety and Efficacy," V. Anderson, editor, *International Journal of Dermatology*, 15 (Supplement): 79–82, 1976.

(4) Herrell, W.E., and D. Heilman, "Experimental and Clinical Studies on Gramicidin," *Journal of Clinical Investigation*, 20:433, 1941.

(5) Dubos, R.J., and R.D. Hotchkiss, "The Production of Bactericidal Substances by Aerobic Sporulating Bacilli," *Journal of Experimental Medicine*, 73:629–640, 1941.

(6) Rammelkamp, C.H., and L. Weinstein, "Hemolytic Effect of Tyrothricin," *Proceedings of the Society for Experimental Biology and Medicine*, 48:211–214, 1941.

(7) Rammelkamp, C.H., and L. Weinstein, "Toxic Effects of Tyrothricin, Gramicidin, and Tyrocidine," *Journal of Infectious Diseases*, 71:166–173, 1942.

(8) Lewis, J.C., et al. "Modification of Gramicidin through Reaction with Formaldehyde," *Science*, 102:274–275, 1945.

(9) Schales, O., and G.E. Mann "Gramicidin Derivatives. I. Preparation; Hemolytic and Bacteriostatic Properties," *Archives of Biochemistry*, 15:357–371, 1947.

(10) Rambhav, S., and L.K. Ramachandran, "The Chemical Modification of Peptide Antibiotics: Part II—The Relative Roles of Ethanolamine and Indole Groupings in the Biological Activity of Gramicidin," *Indian Journal of Biochemistry and Biophysics*, 9:225–229, 1972.

(11) OR 000003, Docket No. 84N–0067, Dockets Management Branch.

9. One comment disagreed with the Category III classification of gramicidin for effectiveness. The comment submitted three studies that it claimed demonstrated the effectiveness of gramicidin (in combination with neomycin) (Refs. 1, 2, and 3) and pointed out that the Panel considered the combination of gramicidin D and neomycin to be rational because it broadens antibacterial coverage against the gram-positive organisms most likely to be found in superficial skin wounds (42 FR 17678).

As additional support for the effectiveness of gramicidin, the comment cited the agency's acceptance of a study by Dillon, Maddox, and Ware (Ref. 4), along with other data, as "sufficient evidence to support the claim 'first aid to help prevent infection in minor cuts, scrapes, and burns' for all topical antibiotics" (47 FR 29992). The comment concluded that "the Panel itself resolved the efficacy issue vis-a-vis gram-positive organisms and the rationality of the combination with neomycin, and the FDA has now ruled in support of the efficacy of all topical antibiotics while simultaneously revising the indication ('first aid to help prevent infection') in a manner that favors use of a potent, anti-gram-positive, non-systemically used antibiotic." The comment further noted that efficacy and safety had been fully discussed in data submitted to FDA

concerning a certified prescription topical product that contains gramicidin, neomycin sulfate, nystatin, and triamcinolone acetonide.

The comment contended that there is adequate support for a Category I designation for gramicidin for use in combination only, as "first aid to help prevent infection in minor cuts, scrapes, and burns." The comment requested that the agency revise § 333.110(c) to include the following: "Gramicidin 0.25 milligrams per gram for use only in combination as provided in section 333.120."

After reevaluating the information on the effectiveness of gramicidin and considering the data cited by the comment, the agency concludes that gramicidin cannot be included in the final monograph as a first aid antibiotic.

One in vivo study cited by the comment (Ref. 1) shows that a combination of neomycin and gramicidin decreases the number of organisms from experimentally induced *Staphylococcus aureus* infections. In the tentative final monograph, the agency cited this study as one of four references to support the conclusion 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." (See 47 FR 29991 to 29992.)

Two of the publications cited by the comment reported the same clinical study (Refs. 2 and 3). In this study, conducted over an 18-month period, 204 children who had sustained major thermal burns received a triple antibiotic cream formulation containing gramicidin, neomycin, and polymyxin B. The results from use of the cream were compared with those from an earlier period without topical chemotherapy against wound infection or with only topical nitrofurazone. The improvement in overall results was significant when the triple antibiotic cream formulation containing gramicidin, neomycin, and polymyxin B was applied topically.

The agency notes that in these studies (Refs. 1, 2, and 3) gramicidin was used in combination with other ingredients, and that there is no evidence to demonstrate the specific contribution that gramicidin made to the combination.

The Panel stated that the gramicidin-neomycin combination "* * * is rational since it broadens antibacterial coverage against the gram-positive organisms most likely to be found in superficial skin wounds, and also decreases the likelihood of encountering a bacterial strain resistant to both antibiotics as well as the chance of developing an infection that might be resistant to both antibiotics" (42 FR 17678). Nevertheless, the Panel concluded that "prudent scientific judgment does not permit the conclusion that merely arguing their efficacy by analogy is sufficient" (42 FR 17678).

The study by Dillon, Maddox, and Ware (Ref. 4), which did not involve gramicidin, was cited by the agency to demonstrate that antibiotics that have been shown to inhibit or to reduce the number of bacteria under non-OTC conditions in induced wounds or in major wounds can also be presumed to be effective in helping to prevent infection under OTC conditions in minor cuts, scrapes, and burns. The agency's statement on this study in the preamble to the tentative final monograph was intended to show that a claim of "first aid to help prevent infection" was appropriate for OTC topical antibiotics that have sufficient effectiveness data. However, it was not intended to justify reclassification of gramicidin (or of any other antibiotics for which there are no in vivo data) into Category I (monograph) status.

In addition, the comment referred to a prescription product that contains neomycin and gramicidin in combination with other ingredients and that is being evaluated under the agency's drug efficacy study implementation (DESI) program). Under DESI, the agency concluded in 1972 that this product was possibly effective for all of its labeled indications relating to use in various dermatoses and as an anti-infective agent (37 FR 12856). Subsequently, the agency concluded that the data on this product did not demonstrate that each component made a significant contribution to the claimed effects of the drug. (See the **Federal Register** of September 25, 1981 (46 FR 47408).) On October 20, 1981, the manufacturer of the product (which also submitted the comment at issue) requested a hearing, and on November 24, 1981, it filed data and other information in support of its hearing request.

After the firm submitted this comment to this OTC drug rulemaking, the agency published a DESI notice to grant the firm a hearing on the proposal to withdraw approval of the new drug applications for the prescription product. (See the **Federal Register** of September 17, 1984; 49 FR 36439.) At a prehearing conference held on January 11, 1985, the agency concluded that the combination drug policy is satisfied with respect to nystatin and triamcinolone acetonide, two of the four ingredients in the prescription product, for the treatment of cutaneous candidiasis, and the company agreed to reformulate the product to delete neomycin and gramicidin (Ref. 5). (See the **Federal Register** of April 17, 1985; 50 FR 15227.)

Therefore, the agency concludes that the evidence submitted to date does not demonstrate that gramicidin (alone or in combination) is effective for use as a first aid antibiotic drug product. The agency recommends that a well-designed, double-blinded study be conducted to show in vivo efficacy of gramicidin by itself or as a contributor to a combination.

Accordingly, gramicidin is not being included in this final monograph.

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(5) OR 000003, Docket No. 84N–0067, Dockets Management Branch.

D. Comments on Combination Drug Products

10. One comment requested that FDA expand the proposed allowable concentrations for bacitracin, bacitracin zinc, and neomycin sulfate to include the concentrations of these ingredients in all combinations currently approved for OTC use in the antibiotic regulations. The comment pointed out that § 448.510e permits a bacitracin concentration of 400 units per g for a combination bacitracin-neomycin sulfate-polymyxin B sulfate ointment, and that § 448.513c permits a bacitracin zinc concentration of 400 units per g and a neomycin sulfate concentration equivalent to 3 mg neomycin for a combination bacitracin zinc-neomycin sulfate-polymyxin B sulfate ointment. The comment stated that it is not clear why these concentrations were omitted from the tentative final monograph. The

comment added that to resolve these conflicts between the OTC topical antibiotic tentative final monograph and the antibiotic regulations, the tentative final monograph should be revised so that bacitracin and bacitracin zinc concentration could be 400 or 500 units per g, and the allowable concentration for neomycin sulfate could be the equivalent of 3 or 3.5 mg neomycin.

As discussed in comment 3 above, the agency is revising the format for listing monograph antibiotic ingredients from that used in the tentative final monograph. In this final monograph, the agency is listing each generally recognized as safe and effective ingredient and the dosage forms of that ingredient that have been specified in the antibiotic regulations. The agency is also revising the combinations of first aid antibiotic drug products to specify the particular antibiotic ingredients, the concentrations permitted for each of these ingredients, and the dosage forms currently identified in the specific monographs in the antibiotic regulations that apply to OTC drug monograph first aid antibiotics. These revisions correct the conflicts in FDA's proposed regulations that the comment pointed out.

11. Two comments disagreed with the agency's decision not to include antibiotic-anesthetic combinations in the tentative final monograph until data were submitted to show that the population that would use these combinations on skin wounds would not be at risk and until information is submitted to show that the combinations meet the criteria in 21 CFR 330.10(a)(4)(iv) (47 FR 29996).

One of the comments stated that, except for a possible safety issue, sufficient information to meet all the remaining criteria of 21 CFR 330.10(a)(4)(iv) is presently in the record. Both comments pointed out that combinations of certain antibiotics and anesthetics are allowed under the antibiotic certification regulations (§§ 444.542a [neomycin sulfate ointment with 200 milligrams benzocaine per gram of ointment]; 444.542j [neomycin sulfate-polymyxin B sulfate-gramicidin ointment with 10 milligrams benzocaine per gram of ointment]; 448.510a [bacitracin ointment with a suitable local anesthetic]; and 448.510e [bacitracin-neomycin sulfate-polymyxin B sulfate ointment with a suitable local anesthetic]), and that Form 6's for products containing these combinations have been approved by FDA for OTC use. One comment also noted that the Topical Analgesic Panel's recommended monograph for OTC external analgesic drug products (44 FR 69768, 69864; December 4, 1979) provides for combinations of many Category I analgesics, anesthetics, or antipruritics with single Category I topical antimicrobial active ingredients or combinations of Category I topical antimicrobial active ingredients.

The comments contended that the agency's concern that the presence of an anesthetic will mask symptoms of infection is unfounded because OTC antibiotics are indicated for "first aid" use and not for the treatment of existing infections. One comment argued that the absence of a safety issue with OTC use of such combinations is demonstrated by the lack of a single adverse reaction report for such products in the records of FDA's Division of Drug Experience. The comment added that 21 CFR 310.300 and 310.301 require that the holder of an approved antibiotic application report adverse reactions to FDA. The comment requested that the agency include any reports of adverse reactions that are in its files in the administrative record of this proceeding as new data for use in determining whether there is any risk to the population in approving OTC antibiotic-analgesic combinations. The comment stated that the absence of adverse reaction reports in FDA's files constitutes data supporting both the general safety of such OTC combination products and the conclusion that masking of infection should not be a concern. The other comment added that the action of the anesthetic ingredient does not persist for the entire 8- to 24-hour period between applications of the product. Thus, the comment argued, it is hardly conceivable that inclusion of the anesthetic could mask symptoms of a worsening infection and present a hazard to consumers.

Concerning the requirements of 21 CFR 330.10(a)(4)(iv), one comment pointed out that only Category I ingredients would be allowed in these combinations, and that the label claim for the product would be to help prevent infection and to provide relief of pain associated with minor wounds. The comment added that the contribution of the respective ingredients to these claimed effects is known, that the combination does not decrease safety or effectiveness, and that such combination therapy would be rational because it is common knowledge that pain usually accompanies minor wounds.

One comment concluded that the antibiotic-anesthetic combinations permitted under the existing antibiotic certification regulations should also be permitted in the OTC first aid antibiotic monograph and requested that the agency provide for such combinations in the final monograph. The other comment further requested that all combinations of Category I first aid antibiotics and Category I local anesthetics be approved as Category I combinations.

Based on the points raised by the comments and after further review as discussed below, the agency has reconsidered its decision in the tentative final monograph and now agrees with the comments that certain topical antibiotic-anesthetic combinations are Category I.

The agency acknowledges that in the tentative final monograph it pointed out that no data on such combinations had been reviewed by the Panel or submitted in comments (47 FR 29996). The agency stated, however, that it was conceivable that the combination could provide rational therapy for OTC use.

Upon further review, the agency finds that the combination of a topical antibiotic with a local anesthetic has had a marketing history that predates the OTC drug review. For example, on June 29, 1972 (37 FR 12857), a notice on certain OTC topical antibiotic products under the DESI program deferred action on these products pending the results of the OTC drug review. This DESI notice included products containing topical antibiotics combined with the local anesthetic benzocaine (four products) or with diperodon hydrochloride (one product). These antibiotic-anesthetic drug products currently have first aid labeling claims, such as "to help prevent infection" and "as an aid for the temporary relief of discomfort in minor cuts, burns, and abrasions." Also, as the comments noted, combinations of certain antibiotics and anesthetics for topical use are currently allowed under the antibiotic certification regulations. A review of the FDA adverse drug reaction reports failed to show any adverse reaction reports for these combinations.

Both the advance notice of proposed rulemaking (44 FR 69865) and the tentative final monograph (48 FR 5852, 5868; February 8, 1983) for OTC external analgesic drug products provide for combinations of Category I external analgesic, anesthetic, or antipruritic ingredients with Category I topical antimicrobial active ingredients. The agency notes that no adverse comments about masking infection or other objections have been received from the medical community regarding the combination in that rulemaking.

Although the tentative final monograph for OTC external analgesic drug products provides only for combinations of Category I external

analgesic, anesthetic, or antipruritic ingredients with Category I topical antimicrobial active ingredients identified in Part 333, Subpart A, the agency believes that combinations with first aid antibiotics (Part 333, Subpart B) are also appropriate. The combination of a first aid antibiotic and an external analgesic, anesthetic, or antipruritic is similar in action and intended use to the combination of a topical antimicrobial and an external analgesic, anesthetic, and antipruritic and will be included in this final monograph for first aid antibiotic drug products.

The agency agrees with the comment that OTC first aid antibiotics are not labeled for the treatment of existing infections and are limited to use on minor injuries for not longer than 1 week with warnings to stop use and to consult a doctor if the condition persists or gets worse. Accordingly, the agency concludes that combinations of first aid antibiotic and local anesthetic ingredients provide rational concurrent therapy for a significant proportion of the target population and that the combination is suitable for OTC use under adequate directions for use and warnings against unsafe use, as required under § 330.10(a)(4)(iv).

The agency proposed in § 348.50(b)(2) of the tentative final monograph for OTC external analgesic drug products (48 FR 5866) the following indication for local anesthetics: "For the temporary relief of" (select one of the following: "pain," "itching," or "pain and itching") (which may be followed by: "associated with" (select one or more of the following) "minor burns," "sunburn," "minor cuts," "scrapes," "insect bites," or "minor skin irritation,")). This indication is very similar to the indication for first aid antibiotics in § 333.150(b) of this final monograph, which reads, "First aid to help * * * prevent" (select one of the following: "infection," "bacterial contamination," or "infection or bacterial contamination") "in minor cuts, scrapes, and burns." Therefore, it would be reasonable for an individual with a minor cut, scrape, or burn to apply both a local anesthetic drug product and a first aid antibiotic drug product to the same minor wound.

First aid antibiotics are included in the monograph based on labeling that they be used only on small areas of the body for a minor cut, scrape, or burn, and that they bear a warning that they not be applied over large areas of the body. Accordingly, those proposed Category I claims for external analgesic drug products that refer to conditions other than minor wounds, and particularly conditions likely to involve large areas of the body (e.g., sunburn), would be nonmonograph for the topical antibiotic-anesthetic combination drug product.

The agency acknowledges the Panel's concern that the addition of an anesthetic to a topical antibiotic drug product could pose safety problems by masking signs of infection. However, the agency believes that appropriate labeling can be written to alleviate this concern. In the tentative final monograph, the agency proposed the following warning in § 333.150(c)(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." The rationale for this warning was discussed in comment 9 of the tentative final monograph (47 FR 29990). The agency believes that this warning adequately informs consumers using these products when to consult a doctor, if necessary, even if the product is an antibiotic-anesthetic combination.

A number of topical antibiotic-anesthetic combinations have been marketed OTC for a number of years under current antibiotic monographs in 21 CFR Parts 444 and 448 (see below). FDA is currently including some of these combinations in this final monograph, as discussed below, so that it conforms to the current antibiotic regulations in the Code of Federal Regulations (CFR).

In conclusion, the agency is including in the final monograph only those topical antibiotic-anesthetic combinations that include Category I ingredients from both the external analgesic and first aid antibiotic rulemakings and that are subject to a current CFR antibiotic monograph with labeling containing adequate directions under which the layman can use the drug safely and efficaciously. The following anesthetic-antibiotic combinations currently have CFR monographs:

Section 444.542a(a)(1)(i)(j)—Neomycin sulfate ointment with benzocaine.

Section 444.542c(a)(1)(i)—Neomycin sulfate lotion with diperodon hydrochloride and aluminum dihydroxyallantoinate.

Section 444.542j—Neomycin sulfate-polymyxin B sulfate-gramicidin-benzocaine ointment.

Section 448.510a—Bacitracin ointment (with a suitable local anesthetic).

Section 448.510e—Bacitracin-neomycin sulfate-polymyxin B sulfate ointment (with a suitable local anesthetic).

Neomycin sulfate lotion combined with the local anesthetic diperodon hydrochloride under § 444.542c is not being included in this final monograph. Diperodon has not been included in the rulemaking for OTC external analgesic drug products. Accordingly, a topical antibiotic-anesthetic combination containing diperodon is not being included in the first aid antibiotic final monograph. Because gramicidin is not included in this final monograph, the combination included in § 444.542j is also not being included in the monograph. Both of these combinations still require a drug application to be marketed.

The agency interprets the term "suitable local anesthetic" as currently specified in § 448.510a and § 448.510e of the antibiotic regulations to mean any of the ingredients identified in § 348.10(a) of the tentative final monograph for OTC external analgesic drug products. These are identified as amine or "caine"-type local anesthetics and include:

(1) Benzocaine 5 to 20 percent.
(2) Butamben picrate 1 percent.
(3) Dibucaine 0.25 to 1 percent.
(4) Dibucaine hydrochloride 0.25 to 1 percent.
(5) Dimethisoquin hydrochloride 0.3 to 0.5 percent.
(6) Dyclonine hydrochloride 0.5 to 1 percent.
(7) Lidocaine 0.5 to 4 percent.
(8) Lidocaine hydrochloride 0.5 to 4 percent.
(9) Pramoxine hydrochloride 0.5 to 1 percent.
(10) Tetracaine 1 to 2 percent.
(11) Tetracaine hydrochloride 1 to 2 percent.

Because the above local anesthetics are not yet subject to a final monograph, FDA cannot refer in this first aid antibiotic final monograph to a final regulation that does not currently exist. Nonetheless, consistent with the approach taken by FDA in the final monograph for OTC antacid drug products (21 CFR 331.15), the agency is listing these combinations in general terms as combinations of drug classes rather than combinations of specific ingredients, because the nonantibiotic ingredients are not yet subject to a final rule. FDA is including the following first aid antibiotic-anesthetic combinations in the final monograph: in § 333.120(b)(1) the combination of bacitracin and any single generally recognized as safe and effective amine or "caine"-type local anesthetic active ingredient and in § 333.120(b)(2) two combinations of bacitracin-neomycin sulfate-polymyxin B sulfate and any single generally recognized as safe and effective amine or "caine"-type local anesthetic active ingredient.

Until the agency makes a determination on which local anesthetic ingredients to include in the final external analgesic monograph, it will take no regulatory action against such products based solely on the combination of ingredients, provided that the combinations are marketed in accordance with this final monograph, contain a local anesthetic as proposed in § 348.10(a) of the tentative final monograph for OTC external analgesic drug products, and are consistent with an antibiotic monograph in 21 CFR Part 444 or Part 448. Products meeting these conditions may be marketed without a drug application.

At this time, because benzocaine is specifically identified as the local anesthetic in a combination that would otherwise have been included in this final monograph, i.e., neomycin sulfate ointment with benzocaine, the agency is likewise withholding action until the external analgesic monograph, which presently proposes to include benzocaine among specific ingredients, is finalized. In the interim, such a combination can continue to be marketed only under a drug application.

When the final monograph for OTC external analgesic drug products is issued, the agency will amend § 333.120(b) (1) and (2) to include the appropriate cross-reference to the local anesthetics included in that monograph. If benzocaine is included in that final monograph, the agency will also amend Part 333 to provide for the neomycin-benzocaine combination.

II. Agency-initiated Changes

1. In the **Federal Register** of April 17, 1985 (50 FR 15107) FDA announced that, under the agency's DESI program, several topical antibiotic drug products that previously were available by prescription had been reformulated, switched from prescription to OTC status, and labeled as first aid antibiotic drug products. These products are bacitracin zinc-polymyxin B sulfate topical powder (§ 448.513d), bacitracin zinc-polymyxin B sulfate topical aerosol (§ 448.513e), and neomycin sulfate-polymyxin B sulfate cream (§ 444.5421). In the **Federal Register** of October 2, 1986 (51 FR 35211), the agency amended the antibiotic drug regulations to provide for a new OTC dosage form of bacitracin-polymyxin B sulfate topical aerosol (§ 448.510f). Because these products are marketed OTC and contain only monograph ingredients, and because CFR antibiotic regulations have been established for these combinations, the agency is including them in this final monograph for OTC first aid antibiotic drug products. Labeling information for these combinations appears in § 333.160 of this final monograph.

One product, described in § 444.5421, was a reformulation of a cream product that originally contained neomycin sulfate, polymyxin B sulfate, and gramicidin. Gramicidin was not included in the reformulated product because of a lack of sufficient evidence to support its effectiveness, either alone or in combination (50 FR 15108). (See also comments 8 and 9 above.) Two products, a powder and an aerosol, described under § 448.513d and § 448.513e, originally contained neomycin sulfate, polymyxin B sulfate, and bacitracin zinc. Neomycin was removed from these products because of concerns about the safety of applying neomycin in aerosol solution or powder dosage forms over extensive burns or wounds (50 FR 15108). Because of these concerns, the agency has determined that neomycin-containing drug products for OTC use should be limited to ointment and cream topical dosage forms. Therefore, neomycin-containing powders and aerosols are not included in this final monograph for OTC first aid antibiotic drug products. In addition, FDA revoked the antibiotic regulation that allowed OTC labeling for a neomycin aerosol product, described in § 444.542d, because this drug product is no longer manufactured (49 FR 34350; August 30, 1984).

2. The agency notes that the labeling directions recommended by the Panel for all topical antibiotics in the advance notice of proposed rulemaking in § 342.50(c) was intended to limit the area of application, namely: "* * * apply a small amount (an amount equal to the surface area of the tip of a finger) directly to the affected area and cover with sterile gauze if desired. May be applied 1 to 3 times daily." (See 42 FR 17681.) In the tentative final monograph, the agency proposed simpler directions that did not limit the amount of product to be applied to an amount equal to the surface area of the tip of a finger (proposed § 333.150(d); 47 FR 29999).

Based on concerns about neomycin toxicity, as discussed below, and to better inform the consumer of the maximum size of an injury that would be suitable for self-treatment, the agency has reevaluated the directions and has decided to adopt directions for use of ointment and cream products based on the Panel's recommendations. These directions, which are set forth in § 333.150(d)(1), state "* * * Apply a small amount of this product (an amount equal to the surface area of the tip of a finger) on the area 1 to 3 times daily * * *."

3. Because powder products and aerosol products are applied in a different manner, the agency has added separate directions for using powders and aerosols in § 333.150(d) (2) and (3).

4. 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 (42 FR 17666). Neomycin sulfate was reclassified as a Category I first aid antibiotic in the tentative final monograph. After reviewing the Panel's report and the comments, the agency concluded that the short-term use of neomycin in minor cuts and burns would not present a toxicologic risk. The agency concurred with the Panel's conclusion that no further toxicologic testing is needed for neomycin for OTC topical use (47 FR 29995).

The agency has further reviewed neomycin toxicity, including ototoxicity (having a deleterious effect upon the eighth nerve or upon the organs of hearing and balance), that may result from administration by any route when systemic absorption occurs, including application to extensive wounds or burns. In most reports of ototoxicity occurring after topical application of neomycin, "topical" has been interpreted in the broadest sense. For example, it has been interpreted to include irrigation of wounds with solutions of neomycin or intraperitoneal and intrapleural instillations and inhalations (Ref. 1). Moreover, the quantities applied have been comparable to those used in systemic therapy (Ref. 1).

There have been isolated reports of deafness resulting from local application of neomycin-containing preparations to treat extensive skin damage from burns or other causes (Refs. 2 through 7). In most of these reports, the neomycin was applied in aerosol preparations (Refs. 2 through 5). In all cases, treatment was for severe conditions, not for OTC uses commonly encountered (i.e., minor cuts, scrapes, and burns), and the amount of drug used was greater than that being proposed for OTC use.

The agency believes that application of neomycin in an ointment or cream topical dosage form to small areas of the body (minor cuts, scrapes, and burns) would not result in significant systemic absorption. Panzer and Epstein (Ref. 8) reported that single external exposure of normal human skin of the entire body of 6 adult male subjects, and portions of the body of 9 other subjects, to neomycin sulfate ointment for 6 hours

did not result in any percutaneous absorption of neomycin sulfate that could be detected by the usual bioassay methods. Bushby (Ref. 9) reported that Leyden found that no significant blood or urine levels of neomycin could be detected in 8 human subjects with at least 50 percent involvement of their body with psoriasis or atopic dermatitis who were treated twice daily for 7 days with 30 g of either a petrolatum ointment containing neomycin-polymyxin B-bacitracin zinc or a cream containing neomycin-polymyxin B-gramicidin.

Livingood (Ref. 10) found that systemic absorption through burns is more likely to reach measurable blood levels when neomycin sulfate in aqueous solution is applied locally as a compress than when neomycin sulfate ointment is topically applied. Livingood determined blood serum levels or neomycin in 16 patients after neomycin ointment and/or neomycin in aqueous solution had been applied to extensive denuded skin surfaces for at least 1 week. Evidence of systemic absorption of neomycin was found in only 2 of these patients, and in both patients neomycin compresses had been applied on a denuded surface that resulted from second and third degree burns and covered about 20 percent of the body.

The agency concludes that the labeling in this final monograph, i.e., warnings against prolonged use of first aid antibiotic drug products and against use on deep extensive wounds, is adequate for all the antibiotics included in the final monograph, including neomycin. However, the agency believes that it is prudent to specify the dose more fully. Accordingly, as discussed above, the agency has revised the directions in this final monograph to limit the size of the area to be treated by directing consumers to apply only an amount of the product equal to the surface of the tip of a finger. (See also part III. paragraph 7, below—SUMMARY OF SIGNIFICANT CHANGES FROM THE PROPOSED RULE.) The agency believes that the labeling (indications, warnings, and directions) required for OTC first aid antibiotic drug products is sufficient to provide adequate information for the safe OTC topical use of neomycin-containing and other first aid antibiotic drug products.

References

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III. Summary of Significant Changes From the Proposed Rule

1. OTC first aid antibiotic drug products that conform to this monograph are exempt from the requirements for approved applications or approved abbreviated applications or for antibiotic batch certification. (See comment 2 above.)

2. The agency is modifying the "scope" that was proposed in § 333.101 of the tentative final monograph. The scope in this final monograph does not include the phrase "the exemptions established in § 433.1, and the applicable sections of Subpart F of Parts 444, 446, and 448." (See comment 3 above.)

3. The agency has reviewed the labeling proposed in the tentative final monograph and has concluded that the indication proposed in § 333.150(b)(1), "First aid to help prevent infection in minor cuts, scrapes, and burns," and the other allowable indications proposed in § 333.150(b)(2) are very similar and should be combined to avoid duplicative words in the labeling. The section entitled "other allowable statements," proposed in § 333.150(b)(3), has not been included in the final monograph in accordance with the current exclusivity policy. (See comment 5 above.) The revised indication is as follows: "First aid to help" [select one of the following: "prevent," ("decrease" ("the risk of" or "the chance of")), ("reduce" ("the risk of" or "the chance of")), "guard against," or "protect against"] [select one of the following: "infection," "bacterial contamination," or "skin infection"] "in minor cuts, scrapes, and burns."

4. The agency has revised the format for listing antibiotic ingredients and combinations of those ingredients in the monograph to specify the particular antibiotic ingredients, the concentrations permitted for each of those ingredients, and the dosage forms currently identified in the specific monographs in the antibiotic regulations that apply to OTC Category I first aid antibiotics. First aid antibiotic drug products in this final monograph include only those products that have established testing methodology in 21 CFR Parts 444, 446, and 448. Consequently, the agency has modified the format of the final monograph from that proposed in the tentative final monograph, in which antibiotics were grouped and combined solely on the basis of antibacterial activity, without consideration of testing methodology. (See comments 3 and 10 above.)

5. The following combinations are being included in this final monograph: Bacitracin-polymyxin B sulfate topical aerosol, bacitracin zinc-polymyxin B sulfate topical aerosol, bacitracin zinc-polymyxin B sulfate topical powder, and neomycin sulfate-polymyxin B sulfate cream. (See part II, paragraph 1 above—AGENCY-INITIATED CHANGES.) Further, directions that are consistent with the labeling of currently marketed products are being provided for aerosol and powder dosage forms. Aerosol products will bear the following statements under the heading "Directions": "Clean the affected area. Spray a small amount of this product on the area one to three times daily. May be covered with a sterile bandage." Powder products will bear the following statements under the heading "Directions": "Clean the affected area. Apply a light dusting of the powder on the area one to three times daily. May be covered with a sterile bandage." Cream products will have the same directions as ointment products.

6. The agency is including in the final monograph several combinations of first aid antibiotics and local anesthetics. These specific combinations are currently provided for in the antibiotic regulations. (See comment 11 above.) These antibiotic-anesthetic drug products currently have first aid labeling claims such as "to help prevent infection and as an aid for the temporary relief of

discomfort in minor cuts, burns, and abrasions." In addition to the required indication contained in § 333.150(b), the agency is providing in this final monograph that products containing first aid antibiotic ingredients combined with a local anesthetic ingredient may contain an additional indication as follows: "First aid for the temporary relief of" (select one of the following: "pain," "discomfort," "pain or discomfort," or "pain and itching") "in minor cuts, scrapes, and burns." (See § 333.160(b)(2).) As discussed in comment 11 above, claims for OTC external analgesic drug products that refer to conditions other than minor wounds, particularly conditions likely to involve large areas of the body (e.g., sunburn), are nonmonograph for the antibiotic-anesthetic combination drug product.

7. The agency has revised the directions for using first aid antibiotic drug products to better inform the consumer of the maximum size of an injury that would be suitable for self-treatment: The directions for ointment and cream products read as follows: " * * * Apply a small amount of this product (an amount equal to the surface area of the tip of a finger) on the area 1 to 3 times daily * * *." (See Part II, paragraph 2, above—AGENCY-INITIATED CHANGES.) Because powder products and aerosol products are applied in a different manner, the directions instruct the consumer to "apply a light dusting of the powder" or to "spray a small amount of this product."

IV. The Agency's Final Conclusions on OTC First Aid Antibiotic Drug Products

Based on the available evidence, the agency is issuing a final monograph establishing conditions under which OTC first aid antibiotic drug products are generally recognized as safe and effective and not misbranded. Specifically, the following ingredients are included in this final rule for OTC first aid antibiotic use: Bacitracin, bacitracin zinc, chlortetracycline hydrochloride, neomycin sulfate, oxytetracycline hydrochloride (for use in combination only), polymyxin B sulfate (for use in combination only), and tetracycline hydrochloride. FDA has determined that the one other ingredient considered in this rulemaking, gramicidin, is a nonmonograph ingredient. Any drug marketed for use as an OTC first aid antibiotic that is not in conformance with the final monograph (21 CFR Part 333, Subpart B) will be considered a new drug within the meaning of section 210(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)) and may not be marketed for this use unless it is the subject of an approved antibiotic application or abbreviated antibiotic application. Conversely, any drug marketed for use as an OTC first aid antibiotic that is in conformance with the final monograph does not need prior approval for marketing.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (47 FR 29986). The agency has examined the economic consequences of this final rule in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this final rule for OTC first aid antibiotic drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act, Pub. L. 96–354. That assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, the requirement for a Regulatory Flexibility Analysis under the Regulatory Flexibility Act does not apply to this final rule for OTC first aid antibiotic drug products because the proposed rule was issued prior to January 1, 1981, and is therefore exempt.

As discussed in the **Federal Register** of July 9, 1982 (47 FR 29998), the agency is removing § 369.6 and portions of §§ 369.20 and 369.21 applicable to OTC first aid antibiotic drug products, because these portions of the regulations are superseded by the requirements of this final monograph (Part 333, Subpart B). The items being removed include the entry for "ANTIBIOTICS FOR EXTERNAL USE FOR PREVENTION OF INFECTION" under § 369.20 and the entries for "ANTIBIOTIC-CONTAINING DRUGS FOR EXTERNAL USE FOR PREVENTION OF INFECTION," "BACITRACIN-CONTAINING OINTMENTS," "BACITRACIN (ZINC BACITRACIN)-POLYMYXIN OINTMENT; BACITRACIN-POLYMYXIN-NEOMYCIN OINTMENT," and "OXYTETRACYCLINE AND POLYMYXIN B SULFATE" under § 369.21. Although other regulations concerning an OTC drug product are usually removed when an applicable final monograph is published, the agency is not removing the sections of the antibiotic regulations in Subpart F of Parts 444, 446, and 448 that apply to the tests and methods of assay for those first aid antibiotics that are contained in the final monograph. Instead, the final OTC drug monograph will cross-reference the tests and methods of assay contained in those parts of the regulations, in compliance with section 507(e) of the act (21 U.S.C. 357(e)). (See comment 3 above.)

List of Subjects

21 CFR Part 333

Labeling, Over-the-counter drugs, First aid antibiotic drug products.

21 CFR Part 369

OTC drugs, Warning and caution statements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations is amended as follows:

1. Part 333 is added to read as follows:

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

Subpart A—[Reserved]

Subpart B—First Aid Antibiotic Drug Products

Sec.
333.101 Scope.
333.103 Definitions.
333.110 First aid antibiotic active ingredients.
333.120 Permitted combinations of active ingredients.
333.150 Labeling of first aid antibiotic drug products.
333.160 Labeling of permitted combinations of active ingredients.

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); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

Subpart A—[Reserved]

Subpart B—First Aid Antibiotic Drug Products

§ 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 and each of the general conditions established in § 330.1.

(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 product consists of any of the following active ingredients within the specified concentration established for each ingredient and in the specified dosage form:

(a) Bacitracin ointment containing, in each gram, 500 units of bacitracin in a suitable ointment base: *Provided,* that it meets the tests and methods of assay in § 448.510a(b).

(b) Bacitracin zinc ointment containing, in each gram, 500 units of bacitracin zinc in a suitable ointment base: *Provided,* that it meets the tests and methods of assay in § 448.513f(b).

(c) Chlortetracycline hydrochloride ointment containing, in each gram, 30 milligrams of chlortetracycline hydrochloride in a suitable ointment base: *Provided,* that it meets the tests and methods of assay in § 446.510(b).

(d) Neomycin sulfate ointment containing, in each gram, 3.5 milligrams of neomycin in a suitable water soluble or oleaginous ointment base: *Provided,* that it meets the tests and methods of assay in § 444.542a(b).

(e) Tetracycline hydrochloride ointment containing, in each gram, 30 milligrams of tetracycline hydrochloride in a suitable ointment base: *Provided,* that it meets the tests and methods of assay in § 446.581d(b).

§ 333.120 Permitted combinations of active ingredients.

The following combinations are permitted provided each active ingredient is present within the established concentration and in the specified dosage form, and the product is labeled in accordance with § 333.160.

(a) *Combinations of antibiotic active ingredients.* (1) Bacitracin-neomycin sulfate ointment containing, in each gram, 500 units of bacitracin and 3.5 milligrams of neomycin in a suitable ointment base: *Provided,* that it meets the tests and methods of assay in § 448.510d(b).

(2) Bacitracin-neomycin sulfate-polymyxin B sulfate ointment containing, in each gram, in a suitable ointment base the following:

(i) 500 units of bacitracin, 3.5 milligrams of neomycin, and 5,000 units of polymyxin B; or

(ii) 400 units of bacitracin, 3.5 milligrams of neomycin, and 5,000 units of polymyxin B;

Provided, that it meets the tests and methods of assay in § 448.510e(b).

(3) Bacitracin-polymyxin B sulfate topical aerosol containing, in each gram, 500 units of bacitracin and 5,000 units of polymyxin B in a suitable vehicle, packaged in a pressurized container with suitable inert gases: *Provided,* that it meets the tests and methods of assay in § 448.510f(b).

(4) Bacitracin zinc-neomycin sulfate ointment containing, in each gram, 500 units of bacitracin and 3.5 milligrams of neomycin in a suitable ointment base: *Provided,* that it meets the tests and methods of assay in § 448.513b(b).

(5) Bacitracin zinc-neomycin sulfate-polymyxin B sulfate ointment containing, in each gram, in a suitable ointment base the following:

(i) 400 units of bacitracin, 3 milligrams of neomycin, and 8,000 units of polymyxin B; or

(ii) 400 units of bacitracin, 3.5 milligrams of neomycin, and 5,000 units of polymyxin B; or

(iii) 500 units of bacitracin, 3.5 milligrams of neomycin, and 10,000 units of polymyxin B;

Provided, that it meets the tests and methods of assay in § 448.513c(b).

(6) Bacitracin zinc-polymyxin B sulfate ointment containing, in each gram, 500 units of bacitracin and 10,000 units of polymyxin B in a suitable ointment base: *Provided,* that it meets the tests and methods assay in § 448.513a(b).

(7) Bacitracin zinc-polymyxin B sulfate topical aerosol containing, in each 90-gram container, 10,000 units of bacitracin and 200,000 units of polymyxin B in a suitable vehicle, packaged in a pressurized container with suitable inert gases: *Provided,* that it meets the tests and methods of assay in § 448.513e(b).

(8) Bacitracin zinc-polymyxin B sulfate topical powder containing, in each gram, 500 units of bacitracin and 10,000 units of polymyxin B in a suitable base: *Provided,* that it meets the tests and methods of assay in § 448.513d(b).

(9) Neomycin sulfate-polymyxin B sulfate ointment containing, in each gram, 3.5 milligrams of neomycin and 5,000 units of polymyxin B in a suitable water miscible base: *Provided,* that it meets the tests and methods of assay in § 444.542e(b).

(10) Neomycin sulfate-polymyxin B sulfate cream containing, in each gram, 3.5 milligrams of neomycin and 10,000 units of polymyxin B in a suitable vehicle: *Provided,* that it meets the tests and methods assay in § 444.5421(b).

(11) Oxytetracycline hyrochloride-polymyxin B sulfate ointment containing, in each gram, 30 milligrams of oxytetracycline and 10,000 units of polymyxin B in a suitable ointment base: *Provided,* that it meets the tests and methods assay in § 446.567b(b).

(12) Oxytetracycline hydrochloride-polymyxin B sulfate topical powder containing, in each gram, 30 milligrams of oxytetracycline and 10,000 units of polymyxin B with a suitable filler: *Provided,* that it meets the tests and methods assay in § 446.567c(b).

(b) *Combinations of first aid antibiotic active ingredients and local anesthetic active ingredients.*

(1) Bacitracin ointment containing, in each gram, 500 units of bacitracin and any single generally recognized as safe and effective amine or "caine"-type local anesthetic active ingredient in a suitable ointment base: *Provided,* that it meets the tests and methods of assay in § 448.510a(b).

(2) Bacitracin-neomycin sulfate-polymyxin B sulfate ointment containing, in each gram, in a suitable ointment base the following:

(i) 500 units of bacitracin, 3.5 milligrams of neomycin, 5,000 units of polymyxin B, and any single generally recognized as safe and effective amine or "caine"-type local anesthetic active ingredient; or

(ii) 400 units of bacitracin, 3.5 milligrams of neomycin, 5,000 units of polymyxin B, and any single generally recognized as safe and effective amine or "caine"-type local anesthetic active ingredient.

Provided, that it meets the tests and methods of assay in § 448.510e(b).

§ 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.* The labeling of the product states, under the heading "Indications," the following: "First aid to help" [select one of the following: "prevent," ("decrease" ("the risk of" or "the chance of")), ("reduce" ("the risk of" or "the chance of")), "guard against," or "protect against"] [select one of the following: "infection," "bacterial contamination," or "skin infection"] "in minor cuts, scrapes, and burns." Other truthful and nonmisleading statements describing only the indications for use that have been established and listed in this paragraph (b), may also be used, as provided in § 330.1(c)(2), subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

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

(1) "For external use only. 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 doctor."

(d) *Directions.* The labeling of the product contains the following statements under the heading "Directions": (1) *For ointment and cream products.* "Clean the affected area. Apply a small amount of this product (an amount equal to the surface area of the tip of a finger) on the area 1 to 3 times daily. May be covered with a sterile bandage."

(2) *For powder products.* "Clean the affected area. Apply a light dusting of the powder on the area 1 to 3 times daily. May be covered with a sterile bandage."

(3) *For aerosol products.* "Clean the affected area. Spray a small amount of this product on the area 1 to 3 times daily. May be covered with a sterile bandage."

(e) The word "doctor" may be substituted for the word "physician" in any of the labeling statements in this subpart.

§ 333.160 Labeling of permitted combinations of active ingredients.

Statements of identity, indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable.

(a) *Statement of identity.* For a combination drug product that has an established name, the labeling of the product states the established name of the combination drug product, followed by the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC drug monographs. For a combination drug product that does not have an established name, the labeling of the product states the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC drug monographs.

(b) *Indications.* The labeling of the product states, under the heading "Indications," the indication(s) for each ingredient in the combination, as established in the "Indications" sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph (b), may also be used, as provided in § 330.1(c)(2), subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) *For permitted combinations identified in § 333.120(a).* The indications in § 333.150 should be used.

(2) *For permitted combinations identified in § 333.120(b).* In addition to the required indication identified in § 333.150, the labeling of the product may state, under the heading "Indications," the following additional indication: "First aid for the temporary relief of" (select one of the following: "pain," "discomfort," "pain or discomfort" or "pain and itching") "in minor cuts, scrapes, and burns."

(c) *Warnings.* The labeling of the product states, under the heading "Warnings," the warning(s) for each ingredient in the combination, as established in the warnings sections of the applicable OTC drug monographs.

(d) *Directions.* The labeling of the product states, under the heading "Directions," directions that conform to the directions established for each ingredient in the directions sections of the applicable OTC drug monographs. When the time intervals or age limitations for administrations of the individual ingredients differ, the directions for the combination product may not exceed any maximum dosage limits established for the individual ingredients in the applicable OTC drug monograph.

PART 369—INTERPRETATIVE STATEMENTS RE WARNINGS ON DRUGS AND DEVICES FOR OVER-THE-COUNTER SALE

2. The authority citation for 21 CFR Part 369 is revised to read as follows:

Authority: Secs. 502, 503, 506, 507, 701, 52 Stat. 1050–1052 as amended, 1055–1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended (21 U.S.C. 352, 353, 356, 357, 371); 21 CFR 5.10 and 5.11.

§ 369.6 [Removed]

3. By removing § 369.6, *Warnings required on certifiable antibiotic exempted from prescription-dispensing requirements.*

§ 369.20 [Amended]

4. In § 369.20 *Drugs; recommended warning and caution statements,* by removing the entry for "ANTIBIOTICS FOR EXTERNAL USE FOR PREVENTION OF INFECTION."

§ 369.21 [Amended]

5. In § 369.21 *Drugs; warning and caution statements required by regulations,* by removing the entries for "ANTIBOTIC-CONTAINING DRUGS FOR EXTERNAL USE FOR PREVENTION OF INFECTION," "BACITRACIN-CONTAINING OINTMENTS," "BACITRACIN (ZINC BACITRACIN)-POLYMYXIN OINTMENT; BACITRACIN-POLYMYXIN-NEOMYCIN OINTMENT," and "OXYTETRACYCLINE AND POLYMYXIN B SULFATE."

Dated: July 31, 1987.

Frank E. Young,

Commissioner of Food and Drugs.

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