DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food And Drug Administration

21 CFR Part 333

[Docket No. 95N–0062]

RIN 0910–AA01

Topical Antimicrobial Drug Products For Over-The-Counter Human Use; Proposed Amendment of Final Monograph for OTC First Aid Antibiotic Drug Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking that would amend the final monograph for over-the-counter (OTC) first aid antibiotic drug products (the regulation that establishes conditions under which these drug products are generally recognized as safe and effective and not misbranded). The amendment would add a warning statement concerning allergic reactions resulting from topical antibiotic drug products containing bacitracin, bacitracin zinc, neomycin, neomycin sulfate, polymyxin B, or polymyxin B sulfate. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments on the proposed regulation by May 14, 1996; written comments on the agency's economic impact determination by May 14, 1996. FDA is proposing that any final rule based on this proposal become effective 12 months after its date of publication in the Federal Register.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD–105),Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2304.

SUPPLEMENTARY INFORMATION:

I. Background

In the Federal Register of December 11, 1987 (52 FR 47312), FDA issued a final monograph for OTC first aid antibiotic drug products in part 333 (21 CFR part 333) subpart B. The monograph provides for single ingredient products containing bacitracin, bacitracin zinc, neomycin, or neomycin sulfate and various combinations containing bacitracin, neomycin sulfate, and polymyxin B sulfate.

FDA has been informed (Ref. 1) that manufacturers of OTC topical antibiotic drug products containing bacitracin zinc, neomycin sulfate, and polymyxin B sulfate voluntarily have added the following information about the possibility of allergic reactions associated with these antibiotics in the warnings for these products: ''Stop use and consult a physician if * * * a rash or other allergic reaction develops. Do not use this product if you are allergic to any of the listed ingredients.'' This allergy warning resulted from an industry task group's review of adverse event reports involving products containing bacitracin zinc, neomycin sulfate, and polymyxin B sulfate. The reports showed that these products have been reported to be associated with hypersensitivity reactions in susceptible individuals and, in rare instances, nonfatal systemic hypersensitivity reactions.

The agency requested that the task group provide these reports for evaluation (Ref. 2), and the industry subsequently submitted them (Ref. 3). The reports included: (1) Listings from FDA's Spontaneous Reporting System (SRS) of adverse experience reports for prescription and OTC drug products containing bacitracin, neomycin, and polymyxin B sulfate, and (2) sublistings of reports of allergic reactions to bacitracin, neomycin, and polymyxin B sulfate in OTC, prescription, unclassified, and all types of products, not just topical first aid antibiotics. The sublistings showed 923 cases of allergic hypersensitivity; 631 related to prescription products, 261 related to OTC products, and 31 that could not be classified from the available information. No deaths attributable to allergic hypersensitivity have been reported from use of any OTC drug products containing these ingredients. Beginning in 1983, the total number of reports of allergic reactions associated with OTC antibiotic drug products containing bacitracin, neomycin, and/or polymyxin B sulfate increased. The industry believed this increase was associated with more OTC topical antibiotic drug products being marketed following publication of the tentative final monograph for these products in 1982. Industry reported that over the past 4 years, the number of units of these products sold per year has been constant at approximately 29 million units per year.

The industry stated that incidence figures cannot be generated from the data because the denominator (total number of exposures) cannot be accurately determined and the numerator may be confounded by over- and/or underreporting of adverse reactions. The industry concluded that reference to the possibility of allergic reactions in the products' label warnings would benefit consumers who use these products.

II. The Agency's Proposal

The agency has reviewed the adverse experience reports and determined that the labeling suggested by the industry would be beneficial to consumers who use these OTC first aid antibiotic drug products. For the OTC drug products, the majority of reports appear to be nonserious skin reactions characterized as either rash or contact dermatitis. No fatalities were reported for OTC drug products; however, the outcome was listed as unknown in the majority of the reports. More than 50 percent of the allergic reactions reported in the SRS involved antibiotic combination products (e.g., containing at least two of the ingredients, bacitracin, polymyxin B sulfate, and/or neomycin). As with all combination products, an adverse effect may be due to one or several of the ingredients in the product. However, the SRS lists allergic (or rash) reports individually for bacitracin and neomycin. The SRS also contains a few such reports for polymyxin B sulfate products singly. In addition, the Physicians' Desk Reference (Ref. 4) lists such allergic reactions for a single-ingredient polymyxin B sulfate powder for parenteral and/or ophthalmic use.

The final monograph for OTC first aid antibiotic drug products, issued on December 11, 1987, did not include an allergy warning for products containing bacitracin, neomycin, and polymyxin B sulfate. Based on the new information provided by industry, showing an increase in the total number of reports of allergic reactions since 1983, the agency is proposing to add a new warning for products containing bacitracin (zinc), neomycin (sulfate), and polymyxin B (sulfate). The warning adds the words ''or if a rash or other allergic reaction develops. Do not use if you are allergic to any of the ingredients.'' in the middle of the existing warning in § 333.150(c)(2) that has been used for all OTC first aid antibiotic drug products for years. The new warning would read:

> Stop use and consult a doctor if the condition persists or gets worse, or if a rash or other allergic reaction develops. Do not use if you are allergic to any of the ingredients. Do not use longer than 1 week unless directed by a doctor.

The agency is including this new warning in proposed § 333.150(c)(3) under the heading *For any product containing bacitracin, bacitracin zinc, neomycin, neomycin sulfate, polymyxin B, and/or polymyxin B sulfate.* The agency is retaining the current warning in § 333.150(c)(2) for products containing chlortetracycline hydrochloride and tetracycline hydrochloride and is adding the heading *For products containing chlortetracycline hydrochloride or tetracycline hydrochloride* to § 333.150(c)(2). Combinations containing oxytetracycline hydrochloride and polymyxin B sulfate in § 333.120(a)(11) and (a)(12) would use the new warning in proposed § 333.150(c)(3).

Manufacturers of OTC topical first aid antibiotic drug products containing bacitracin, bacitracin zinc, neomycin, neomycin sulfate, and/or polymyxin or polymyxin B sulfate are encouraged to voluntarily implement this labeling addition as of the date of publication of this proposal, subject to the possibility that FDA may change the wording of the warning statement as a result of comments filed in response to this proposal. Manufacturers may include this labeling under the heading ''FDA APPROVED INFORMATION'' in accord with § 330.1(c)(2) (21 CFR 330.1(c)(2)) if that heading is used in product labeling. Because FDA is encouraging that the proposed additional warning statement be used on a voluntary basis at this time, the agency advises that manufacturers doing so will be given ample time after publication of a final rule to use up any labeling implemented in conformance with this proposal.

III. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

(1) Letter dated June 20, 1992, from R. W. Soller, Nonprescription Drug Manufacturers Association, to W. E. Gilbertson, FDA, in OTC Vol. 190036, Docket No. 95N–0062, Dockets Management Branch.

(2) Letter dated July 22, 1992, from W. E. Gilbertson, FDA, to R. W. Soller, Nonprescription Drug Manufacturers Association, in OTC Vol. 190036, Docket No. 95N–0062, Dockets Management Branch.

(3) Letter dated October 7, 1992, from R. W. Soller, Nonprescription Drug Manufacturers Association, to W. E. Gilbertson, FDA, in OTC Vol. 190036, Docket No. 95N–0062, Dockets Management Branch.

(4) Physicians' Desk Reference, 48th ed., Medical Economics Co., Montvale, NJ, p. 738, 1994.

IV. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96–354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the proposed rule is not a significant regulatory action as defined by the Executive Order and, thus, is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. The proposed rule is estimated to generate a one-time label modification, the cost of which will not be significant. Similarly, the costs incurred by small businesses are estimated to be insufficient to warrant a regulatory flexibility analysis. FDA believes that small marketers use relatively simple and inexpensive packaging and labeling. Hence, labeling change costs (for one warning) to small firms are not expected to be substantial. Accordingly, the agency certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on manufacturers of OTC first aid antibiotic drug products that contain bacitracin (zinc), neomycin (sulfate), and/or polymyxin B (sulfate). Comments regarding the impact of this rulemaking on such manufacturers should be accompanied by appropriate documentation. The agency is providing a period of 90 days from the date of publication of this proposed rulemaking in the Federal Register for comments to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

V. Paperwork Reduction Act of 1995

FDA tentatively concludes that the labeling requirement proposed in this document is not subject to review by the Office of Management and Budget because it does not constitute a ''collection of information'' under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the proposed warning statement is a ''public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public'' (5 CFR 1320.3(c)(2)).

VI. Environmental Impact

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

Interested persons may, on or before May 14, 1996, submit written comments to the Dockets Management Branch (address above). Written comments on the agency's economic impact determination may be submitted on or before May 14, 1996. Three copies of all comments are to be submitted, except that individuals may submit one copy. Comments 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. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 333

Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 333 be amended as follows:

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

1. The authority citation for 21 CFR part 333 continues to read as follows:

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

2. Section 333.150 is amended by adding a heading to paragraph (c)(2) and by adding new paragraph (c)(3) to read as follows:

§ 333.150 Labeling of first aid antibiotic drug products.

* * * * *

(c) * * *

(2) *For products containing chlortetracycline hydrochloride or tetracycline hydrochloride.* * * *

(3) *For any product containing bacitracin, bacitracin zinc, neomycin, neomycin sulfate, polymyxin B and/or polymyxin B sulfate.* ''Stop use and consult a doctor if the condition persists or gets worse, or if a rash or other allergic reaction develops. Do not use this product if you are allergic to any of the ingredients. Do not use longer than 1 week unless directed by a doctor.''

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Dated: February 6, 1996.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

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