DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 78N-0196]

Oral Mucosal Injury Drug Products for Over-the-Counter Human Use; Oral Wound Healing Drug Products for Over-the-Counter Human Use

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule establishing that any oral wound healing drug product for over-the-counter (OTC) human use is not generally recognized as safe and effective, is misbranded, and is subject to regulatory action unless it has an approved new drug application (NDA). (Oral wound healing agents are drugs used to aid in the healing of minor oral wounds by means other than cleansing and irrigating, or by serving as a protectant.) After considering the agency's proposed regulation, which was issued in the form of a tentative final monograph, and because no new data or information were submitted, the agency is issuing this final rule to remove oral wound healing agents from the OTC market. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: July 18, 1987.

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

SUPPLEMENTARY INFORMATION: In the **Federal Register** of November 2, 1979 (44 FR 63270), 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 oral mucosal injury drug products, together with the recommendations of the Advisory Review Panel on OTC Dentifrice and Dental Care 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 January 24, 1980. Reply comments in response to comments filed in the initial comment period could be submitted by February 25, 1980.

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 regulation, in the form of a tentative final monograph, for OTC oral mucosal injury drug products was published in the **Federal Register** of July 26, 1983 (48 FR 33984). Interested persons were invited to file by September 26, 1983, written comments, objections, or requests for an 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 23, 1983. New data could have been submitted until July 26, 1984, and comments on the new data until September 26, 1984.

No comments, objections, requests for an oral hearing, or new data were submitted in response to the proposed regulation on OTC oral mucosal injury drug products.

The agency is also engaged in a rulemaking on OTC oral health care drug products to be published in a future issue of the **Federal Register**. Oral health care drug products are used for the temporary relief of symptoms of the mouth and throat, for example, occasional minor sore throat or mouth soreness. The tentative final monograph for OTC oral mucosal injury drug products included two classes of products: oral wound cleansers and oral wound healing agents. There is considerable overlap between the rulemaking on OTC oral mucosal injury drug products and the rulemaking on OTC oral health care drug products. Accordingly, the agency is incorporating that part of the oral mucosal injury rulemaking that covers oral wound cleansers into the first segment of the tentative final monograph for OTC oral health care drug products. That monograph covers OTC anesthetic/analgesic, astringent, debriding agent/oral wound cleanser, and demulcent drug products. An intent of both rulemakings is to identify those ingredients that are generally recognized as safe and effective in temporarily relieving the symptoms of minor oral wounds or other irritations of the mouth or gums.

Carbamide peroxide, hydrogen peroxide, and sodium perborate monohydrate, the three ingredients included in the tentative final monograph for OTC oral mucosal injury drug products as oral wound cleansers, were also included in the rulemaking for OTC oral health care drug products as debriding agents (agents which cause the removal of foreign material or devitalized or contaminated tissue from or adjacent to a traumatic or infected lesion to expose surrounding healthy tissue (47 FR 22927)). A number of the comments submitted to the advance notice of proposed rulemaking for OTC oral health care drug products pointed out the similarities between oral wound cleansers and debriding agents and requested that the labeling for these ingredients be consistent between the two rulemakings. In order to achieve this consistency, the agency has decided to combine debriding agents and oral wound cleansers into one therapeutic class and to include that therapeutic class in the tentative final monograph for OTC oral health care anesthetic/analgesic, astringent, debriding agent/oral wound cleanser, and demulcent drug products. That tentative final monograph will be published in another issue of the **Federal Register**. Final agency action on OTC oral wound healing drug products occurs with the publication of this document.

In the proposed rule on OTC oral mucosal injury drug products (48 FR 33988), the agency accepted the Panel's recommended Category III classification of oral wound healing agents because there were insufficient data to establish safety and effectiveness of these ingredients, and no comments were received on the issue. In this final rule, no ingredients intended for use as an oral wound healing agent have been determined to be generally recognized as safe and effective for OTC use. This final rule declares any product intended for use as an OTC oral wound healing agent to be a new drug under section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)),

for which an NDA approved under section 505 of the act (21 U.S.C. 355) and 21 CFR Part 314 is required for marketing. In the absence of an approved NDA, products intended for this use would also be misbranded under section 502 of the act (21 U.S.C. 352). This final rule amends 21 CFR Part 310 to include OTC oral wound healing agents by adding to Subpart E new § 310.534 (21 CFR 310.534). The inclusion of OTC oral wound healing agents in Part 310 is consistent with FDA's established policy for regulations in which there are no monograph conditions. (See e.g., §§ 310.510, 310.519, 310.525, 310.526, and 310.533.) If, in the future, any ingredient is determined to be generally recognized as safe and effective as an OTC oral wound healing agent, the agency will promulgate an appropriate regulation at that time.

The OTC procedural regulations (21 CFR 330.10) have been revised to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). (See the **Federal Register** of September 29, 1981; 46 FR 47730.) The court in *Cutler* held that the OTC drug review regulations were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision has been deleted from the regulations, which 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.

Although it was not required to do so under *Cutler*, 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).

The agency is aware that products containing certain ingredients offered as oral wound healing agents may have to be reformulated and/or relabeled. The agency has established a period of 12 months after the date of publication of the final rule in the **Federal Register** for reformulation and/or relabeling of products. On or after July 18, 1987, no OTC drug product that is subject to this final rule and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved NDA.

I. Summary of Significant Changes From the Proposed Rule

Oral wound cleansers are being combined with oral health care debriding agents into one therapeutic class that is included in the first segment of the tentative final monograph for OTC oral health care drug products. That tentative final monograph covers OTC anesthetic/analgesic, astringent, debriding agent/oral wound cleanser, and demulcent drug products. It will be published in a future issue of the **Federal Register**. Therefore, those portions of Part 353 (proposed in the **Federal Register** of July 26, 1983; 48 FR 33984) applicable to oral wound cleansers, i.e., definitions proposed in § 353.3; indications, warnings, and directions proposed in § 353.50; and the professional labeling proposed in § 353.80, are being incorporated into the tentative final monograph for OTC oral health care anesthetic/analgesic, astringent, debriding agent/oral wound cleanser, and demulcent drug products. The agency is deferring consideration of proposed § 353.20(b), regarding the combination of an oral wound cleanser and an antiseptic, to the second segment of the OTC oral health care rulemaking, which covers antimicrobial drug products and which will be published in a future issue of the **Federal Register**.

The remaining portion of proposed Part 353 relating to oral wound healing agents, i.e., proposed §§ 353.3(d), 353.20 (a) and (c), and 353.50(a) will not be addressed in an OTC final monograph. No OTC oral wound healing agent has been found to be generally recognized as safe and effective and not misbranded. Oral wound healing agents are now considered to be new drugs. Accordingly, this final rule or oral wound healing agents is being promulgated under 21 CFR Part 310 rather than under 21 CFR Part 330. Therefore, the agency is amending Part 310 to include a final rule declaring OTC oral wound healing agents to be new drugs, by adding to Subpart E new § 310.534.

II. The Agency's Final Conclusions on OTC Oral Wound Healing Drug Products

The agency has determined that no ingredient has been found to be generally recognized as safe and effective for use as an OTC oral wound healing agent. Therefore, all oral wound healing agents, including those reviewed by the Panel, i.e., allantoin, carbamide peroxide in anhydrous glycerin, water soluble chlorophyllins, and hydrogen peroxide in aqueous solution, are considered nonmonograph ingredients. Any OTC drug product that is labeled, represented, or promoted for use as an oral wound healing agent is misbranded under section 502(a) of the act (21 U.S.C. 352(a)) and is a new drug within the meaning of section 201(p) of the act.

The agency is aware that products containing some of the above ingredients have been on the OTC market and that these products have had multiple claims. Purported oral wound healing agents must be removed from these OTC drug products or the product must be relabeled to exclude oral wound hearing claims by the effective date of this final rule unless the product has an approved NDA.

In response to the agency's request for specific comment on the economic impact of this rulemaking (48 FR 33984), no comments were received. 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 those rules, including this final rule for OTC oral wound healing 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, this particular rulemaking for OTC oral wound healing agents is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

List of Subjects in 21 CFR Part 310

New drugs

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act and under 21 CFR 5.11, Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations is amended in Part 310 as follows:

PART 310—NEW DRUGS

1. The authority citation for Part 310 continues to read as follows:

Authority: Secs. 502, 503, 505, 701, 52 Stat. 1051, 1052, 1053, 1055 as amended (21 U.S.C. 352, 353, 355, 371) (5 U.S.C. 553); 21 CFR 5.11.

2. In Subpart E by adding new § 310.534 to read as follows:

§ 310.534 Drug products containing active ingredients offered over-the-counter (OTC) for human use as oral wound healing agents.

(a) Allantoin, carbamide peroxide in anhydrous glycerin, water soluble chlorophyllins, and hydrogen peroxide in aqueous solution have been present in oral mucosal injury drug products for use as oral wound healing agents. Oral wound healing agents have been marketed as aids in the healing of minor oral wounds by means other than cleansing and irrigating, or by serving as a protectant. Allantoin, carbamide peroxide in anhydrous glycerin, water soluble chlorophyllins, and hydrogen peroxide in aqueous solution are safe for use as oral wound healing agents, but there are inadequate data to establish general recognition of the effectiveness of these ingredients as oral wound healing agents.

(b) Any OTC drug product that is labeled, represented, or promoted for use as an oral wound healing agent is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act, for which an approved new drug application under section 505 of the act and Part 314 of this chapter is required for marketing. In the absence of an approved new drug application, such product is also misbranded under section 502 of the act.

(c) A completed and signed "Notice of Claimed Investigational Exemption for a New Drug" (Form FDA–1571) (OMB Approval No. 0910–0014), as set forth in § 312.1 of this chapter, is required to cover clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted OTC as an oral wound healing agent is safe and effective for the purpose intended.

(d) After the effective date of the final regulation, any OTC drug product that is labeled, represented, or promoted for use as an oral wound healing agent may not be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved new drug application.

Dated: March 5, 1986.

Frank E. Young,

Commissioner of Food and Drugs.

Otis R. Bowen,

Secretary of Health and Human Services.

[FR Doc. 86–16181 Filed 7–17–86; 8:45 am]

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