DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 353

[Docket No. 78N-0196]

Oral Mucosal Injury Drug Products for Over-the-Counter Human Use; Tentative Final Monograph

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 in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) oral mucosal injury drug products (drug products which relieve oral soft tissue injury by cleansing or promoting the healing of minor oral wounds of irritations) are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drug by September 26, 1983. New data by July 26, 1984. Comments on the new data by September 26, 1984. These dates are consistent with the time periods specified in the agency's revised procedural regulations for reviewing and classifying OTC drugs (21 CFR 330.10). Comments on the agency's economic impact determination by November 23, 1983.

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

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, National Center for Drugs and Biologics (HFN-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

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 public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information. In response to the advance notice of proposed rulemaking, the Panel Chairman, one drug manufacturers' association, five drug manufacturers, and two individual consumers submitted comments. Copies of the comments received are on public display in the Dockets Management Branch.

The advance notice of proposed rulemaking, which was published in the Federal Register on November 2, 1979 (44 FR 63270), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the present document is designated in the OTC drug review regulations as a "tentative final monograph." Its legal status, however, is that of proposed rule. In this tentative final monograph (proposed rule) to establish Part 353 (21 CFR Part 353) the FDA states for the first time its position on the establishment of a monograph for OTC oral mucosal injury drug products. Final agency action on this matter will occur with the publication at a furture date of a final monograph, which will be a final rule establishing a monograph for OTC oral mucosal injury drug products.

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

The 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 OTC drug rulemaking process before the establishment of a final monograph.

Although it was not required to do so under *Cutler*, FDA will no longer use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but will use instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the Federal Register. On or after that date, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved new drug application. Further, any OTC drug products subject to this monograph that are repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initiallly introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In the advance notice of proposed rulemaking for OTC oral mucosal injury drug products (published in the **Federal Register** of November 2, 1979 (44 FR 63270)), the agency suggested that the conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the **Federal Register** and that the conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of whether further testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

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

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

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notice published in the **Federal Register** of January 30, 1973 (38 FR 2781) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

I. The Agency's Tentative Conclusions on the Comments

A. General Comments on Oral Mucosal Injury 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 rulemaking proceedings.

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

2. One comment noted that the Panel's definition of "prophylactic" contains the word "preventative" as a synonym for "prophylactic." However, the comment stated that the word "preventative" is a noun, whereas "prophylactic" is an adjective, so that these two words are not synonymous. The comment suggested that correct usage would be to state that "prophylactic" is synonymous with "preventive" rather than "preventative."

The words "prophylactic" and "preventative" each can be properly used as a noun and an adjective (Ref. 1). Therefore, the Panel was correct in considering the two terms to be synonymous.

Reference

(1) Webster's Third New International Dictionary, G. & C. Merriam Company, Springfield, Mass., 1976, s.v. "preventative" and "prophylactic."

B. Comments on Specific Oral Mucosal Injury Active Ingredients

3. One comment cited a newspaper article on the Panel's report which stated that the Panel recommended peroxide as the only nonprescription substance that can safely and effectively clean mouth and gum injuries. The comment stated that while peroxide may be the only drug product sold without prescription, one teaspoon of salt dissolved in a glass of warm water and used as a mouth wash is a very effective substance. The comment added that the salt solution not only helps clean the mouth, but also toughens the gums, helps to heal the gums after tooth extraction, and helps to heal bleeding gums. The comment also stated that a certain commercial drug product (containing camphor and phenol) was effective in relieving pain of sore gums.

The Panel classified 1.5 to 3 percent hydrogen peroxide in aqueous solution and 10 percent carbamide peroxide in anhydrous glycerin as Category I OTC oral wound cleansers. The agency agrees with the Panel's recommendations. The Panel did not receive any data on the use of salt in warm water for the uses claimed by the comment and did not discuss the use of salt solution as an oral wound cleanser or oral wound healing agent. The comment also did not submit any data. Camphor and phenol, the ingredients in the commercial drug product mentioned by the comment, were reviewed by the Panel as oral mucosal analgesics in its report on drug products for relief of oral discomfort. (See the **Federal Register** of May 25, 1982; 47 FR 22712.) The agency will consider the combination of these ingredients for relief of the pain of sore gums in its tentative final monograph on drug products for relief of oral discomfort, which will be published in a future issue of the **Federal Register.**

4. Three comments objected to the Panel's recommendation to place sodium perborate monohydrate in Category II as an oral wound cleanser. To support their requests for Category I status, all of the comments submitted data emphasizing the safety of sodium perborate monohydrate when used as a mouthrinse.

One of the comments stated that the majority of boron toxicity incidents cited in the literature involve direct application of borates to open wounds or ingestion by infants under 1 year of age. Another of the comments maintained that the Panel's literature references on sodium perborate toxicity were related to early reports of the action of boric acid and boric acid salts

when misused as antiseptics. The comment added that literature references cited by the Panel regarding irritating effects attributed to the use of sodium perborate (e.g., chemical burns, hairy tongue, and edema of the lips) were taken from publications more than 40 years old that actually dealt with the excessive use of unbuffered sodium perborate, not with the proper use of sodium perborate monohydrate. The comment cited 30 years of marketing experience of sodium perborate monohydrate mouthrinse without a related occurrence of any of these adverse effects.

The comment maintained that the Panel had made an inaccurate assessment of the potential risk of boron poisoning when sodium perborate monohydrate is used as an oral wound cleanser. Although the Panel concluded that the maximum safe dose of boron for ingestion by adults is 90 milligrams (mg) per day (44 FR 63282), the comment pointed out that a considerable difference of opinion exists regarding the toxicity of boron in humans. The comment added that, when properly used, sodium perborate monohydrate mouthrinse actually delivers much less than 90 mg boron per day and that the level of boron absorption is very low.

The comment contended that the Panel's Category II classification of sodium perborate monohydrate is inconsistent with the action of other panels (e.g., the Advisory Review Panel on OTC Ophthalmic Drug Products, the Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products, and the Dental Device Panel (Bureau of Medical Devices)) that permitted boron in OTC products even when its presence was not strictly considered a pharmaceutical necessity. The comment also expressed concern that the Panel's classification of sodium perborate monohydrate in Category II was based upon its interpretation of a request from the Committee on Drugs of the American Academy of Pediatrics. The comment pointed out that, in a January 25, 1974 letter to the Commissioner, the Committee requested that FDA "take action to remove boric acid and boric acid salts from all over-the-counter products unless they have been shown to be necessary to the efficacy of the product" (Ref. 1), and the Panel had apparently interpreted this as a request to remove all boron-containing products from the OTC market.

The comment asserted that the Panel's recommendation at 44 FR 63281 that an oral wound cleanser must deliver 1.5 to 3 percent hydrogen peroxide to be effective is arbitrary and undocumented. The comment stated that there are no data showing that a product containing an amount of sodium perborate monohydrate that breaks down in water to deliver 1.3 to 1.4 percent hydrogen peroxide is a less effective oral wound cleanser than a solution of at least 1.5 percent hydrogen peroxide.

The agency has reviewed the Panel's recommendations and the additional data submitted by the comments and concludes that the data demonstrate the safety of sodium perborate monohydrate when used as an oral wound cleanser. One study showed that 6 months' use of sodium perborate as a tooth powder produced no irritating effects in the subjects (Ref. 2). Two studies showed that very little boron is absorbed into the blood after use of sodium perborate monohydrate as a mouthrinse (Refs. 3 and 4). A human retention study established the mean quantity or boron left behind in the mouth after use of a sodium perborate monohydrate mouthrinse as 5 mg per rinse (or 20 mg per day if one rinses four times a day) (Ref. 5). Acute, subacute, and chronic toxicity studies showed minimal adverse reactions when various boron compounds were administered orally or intravenously to laboratory animals (Refs. 6, 7, and 8). Three literature reviews on the toxicology of boron compounds stressed their relative nontoxicity to humans and noted that the acute lethal dose of boric acid and its salts in humans varies from 3 grams (g) for infants to 45 g for an adult, suggesting that boron is relatively more toxic to children (Refs. 9, 10, and 11).

Data compiled by the National Clearinghouse for Poison Control Centers showed only 26 accidental ingestions of sodium perborate monohydrate (including 10 in children under 5 years of age) over a 9-year period. In the 26 reported ingestions, there were only two reports of symptoms, neither of which occurred in children under 5 years of age. There were no hospitalizations and no fatalities (Ref. 12).

Following the April 28, 1978 adoption of the Panel's report, the Committee on Drugs of the American Academy of Pediatrics submitted a letter of clarification to FDA, dated July 18, 1978, stating in part that the sodium perborate monohydrate component was necessary for the efficacy of a product submitted to the Panel for review as on oral wound cleanser (Ref. 13). The agency concurs.

The agency believes that there is sufficient evidence to support a dose of sodium perborate monohydrate that releases 1.3 to 1.4 percent hydrogen peroxide in the mouth. Oral wound cleansing by a hydrogen peroxide-containing compound is a physical pheomenon based on its foaming activity in the mouth that results from the release of molecular oxygen when hydrogen peroxide comes into contact with tissue or salivary catalase. This foaming action loosens and lifts out debris, thus cleansing the wound. The measurement of doses of hydrogen peroxide may be variable and, therefore, the amount of molecular oxygen released is also variable, depending upon the quantity of rinse in a person's mouth. Therefore, based upon these facts and the long marketing history of the ingredient, the agency believes that a lower limit of 1.3 percent for the effectiveness of hydrogen peroxide as an oral wound cleanser is justified.

Based on its evaluation of the submitted documents, including data not available to the Panel, and the long history of safe marketing of sodium perborate monohydrate, the agency concludes that sufficient evidence exists to support the reclassification of 1.2 g sodium perborate monohydrate in aqueous solution (dissolved in approximately 20 milliliters (mL) of warm water) for use up to four times daily, from Category II to Category I when used as an oral wound cleanser.

Because some reports suggest that boron is more toxic to children than to adults (Refs. 9, 10, and 11), and children are more likely to swallow the rinse (44 FR 63278), oral wound cleansing products containing sodium perborate monohydrate should be labeled not for use by children under 6 years of age unless directed by a dentist or doctor. In addition, the agency is proposing that dosage units be limited to not more than 1.2 g sodium perborate monohydrate. The agency, therefore, is proposing the following directions in this tentative final monograph for products containing sodium perborate monohydrate:

For use as an oral rinse. Dissolve 1.2 grams of sodium perborate monohydrate in 1 ounce (30 milliliters) of warm water. Use immediately. Swish solution around in the mouth over the affected area for at least 1 minute and then spit it out. Do not swallow. Use up to four times daily after meals and at bedtime or as directed by a dentist or doctor. Children under 12 years of age should be supervised in the use of this product. Children under 6 years of age: Consult a dentist or doctor.

The agency is also proposing that the Category I indication for use in the cleansing of gum irritation due to erupting teeth (teething), in § 353.50(b)(1)(ii) of the Panel's proposed

monograph, be classified as Category II labeling for oral wound cleansers containing sodium perborate monohydrate because teething occurs in children at an age that is contraindicated for the use of sodium perborate monohydrate. The agency is proposing a professional labeling section in this tentative final monograph, § 353.80, that contains the indication for the use of oral wound cleansers other then sodium perborate monohydrate for the cleansing of gum irritation due to teething. The agency believes that such usage should be under the direction of a doctor or dentist.

The agency's detailed comments and evaluations on the data are on file in the Dockets Management Branch (Ref. 14).

References

(1) Letter from S. J. Yaffe, American Academy of Pediatrics, to the Commissioner, FDA, Comment No. C00003, Docket No. 78N–0196, Dockets Management Branch.

(2) Bodecker, C. F., and L. R. Cahn, "Effect of Daily Use of Flavored Sodium Perborate as a Dentifrice for a Six Months Period," *Journal of Dental Research*, 17:161–172, 1938.

(3) Edwall, L., B. Karlen, and A. Rosen, "Absorption of Boron after Mouthwash Treatment with Bocosept," *European Journal of Clinical Pharmacology*, 15:417–420, 1979.

(4) Dill, H., B. Gmeiner, and W. Raab, "Blood Boron Levels in Patients Using Buffered Sodium Peroxyborate Monohydrate Mouthwash Three Times Daily for Four Weeks," *International Journal of Clinical Pharmacology*, 15:16–18, 1977.

(5) Stuchell, R., "Final Report on Boron Retention after Rinsing the Mouth with Amosan," Comment No. C00003, Docket No. 78N–0196, Dockets Management Branch.

(6) Mulinos, M. G., G. K. Higgins, and G. J. Christakis, "On the Toxicity of Sodium Perborate," *Journal of the Society of Cosmetic Chemists*, 3:297–302, 1952.

(7) Weir, R. J., and R. S. Fisher, "Toxicological Studies on Borax and Boric Acid," *Toxicology and Applied Pharmacology*, 23:351–364, 1972.

(8) Miller, S. A., "Preliminary Report on Amosan Toxicity Study," Comment No. C00003, Docket No. 78N–0196, Dockets Management Branch.

(9) Pfeiffer, C. C., and E. H. Jenney, "The Pharmacology of Boric Acid and Boron Compounds," *Bulletin of the National Formulary Committee*, American Pharmaceutical Association, 18:57–80, 1950.

(10) Griffin, T. S., "The Toxicity of Boric Acid and Sodium Tetraborate: A Literature Review," Comment Nos. C00003 and C00005, Docket No. 78N–0196, Dockets Management Branch.

(11) Brendle-Neher, T., "Toxicology," Comment No. C00003, Docket No. 78N–0196, Dockets Management Branch.

(12) A List of Sodium Perborate Monohydrate Ingestions Compiled by the National Clearinghouse for Poison Control Centers, Bureau of Drugs, Bethesda, MD 20016, Attachment No. 5, Comment No. C00003, Docket No. 78N–0196, Dockets Management Branch.

(13) Letter from J. D. Lockhart, American Academy of Pediatrics, to M. M. Freeman, FDA, Comment No. C00003, Docket No. 78N–0196, Dockets Management Branch.

(14) Letter from W. E. Gilbertson, FDA, to D. Lauck, CooperCare, coded LET, Docket No. 78N–0196, Dockets Management Branch.

C. Comments on Dosages for Oral Mucosal Injury Active Ingredients

5. One comment suggested expanding recommended § 353.10(a)(1), which states "carbamide peroxide 10 percent in anhydrous glycerin," by adding the words "either as a liquid or gel."

The form of the vehicle is not relevant to the safety or effectiveness of this active ingredient; and in the absence of restrictive language in the monograph, either a liquid or gel dosage form can be used. Therefore, the change recommended by the comment is unnecessary.

6. Two comments objected to the Panel's omission of directions for use as an oral rinse of drug products containing carbamide peroxide in anhydrous glycerin. Pointing out that labeling submitted to the Panel for carbamide peroxide in anhydrous glycerin included provision for such use and that the Panel's recommended monograph allows for use of hydrogen peroxide both by direct application and as an oral rinse, the comments requested that directions for use of carbamide peroxide as an oral rinse be added to the mongraph. One comment suggested the following wording for the directions: "For use as an oral rinse, place 10–20 drops onto tongue. Mix with saliva. Swish around in the mouth over the affected area for at least one minute and then spit out. Use up to four times daily after meals and at bedtime, or as directed by a dentist or a physician. Children under 12 years of age should be supervised in the use of this product. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician."

The agency agrees that the directions for use of carbamide peroxide should include instructions for use as an oral rinse and accepts the comment's suggested wording with some modifications. The agency proposes to add the following directions for carbamide peroxide in anhydrous glycerin under § 353.50(d)(1)(ii) in this tentative final monograph:

For use as an oral rinse. Place 10 to 20 drops onto tongue. Mix with saliva. Swish around in the mouth over the affected area for at least 1 minute and then spit out. Use up to four times daily after meals and at bedtime, or as directed by a dentist or a doctor. Children under 12 years of age should be supervised in the use of this product. Children under 2 years of age: consult a dentist or doctor.

D. Comments on Labeling of Oral Mucosal Injury Drug Products

7. One comment stated that FDA lacks statutory authority to prescribe exclusive lists of terms from which indications for use for OTC drug products must be drawn and to prohibit labeling terminology which is truthful, accurate, not misleading, and intelligible to the consumer.

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

During the course of the review, FDA's position on the "exclusivity rule" has been questioned many times in comments and objections filed in response to particular proceedings and in correspondence with the agency. The agency has also been asked by The Proprietary Association to reconsider its position. To assist the agency in resolving this issue, FDA conducted an open public forum on September 29, 1982, at which interested parties presented their views. The forum was a legislative type administrative hearing under 21 CFR Part 15 that was held in response to a request for a hearing on the tentative final monographs for nighttime sleep-aids and stimulants (published in the Federal Register of June 13, 1978; 43 FR 25544). Details of the hearing were announced in a notice published in the Federal Register of July 2, 1982 (47 FR 29002). The agency's

decision on this issue will be announced in the **Federal Register** following conclusion of its review of the material presented at the hearing.

8. One comment disagreed with the Panel's recommendation that inactive ingredients be listed in the labeling of OTC oral mucosal injury drug products. The comment stated that a list of inactive ingredients in the labeling would be meaningless, confusing, and misleading to most consumers. The comment noted that the act does not require that inactive ingredients of drug products be included on a label and argued that requiring the listing of these ingredients in descending order of quantity poses additional problems because labels would have to be changed as quantities of inactive ingredients change.

The agency agrees with the Panel's recommendation. Although the act does not require the complete identification of inactive ingredients in the labeling of OTC drug products, section 502(e) (21 U.S.C. 352(e)) does require disclosure of certain ingredients, whether included as active or inactive components in a product. In the absence of authority to require the inclusion of all the inactive ingredients in OTC drug product labeling, the agency urges manufacturers to list all inactive ingredients voluntarily as suggested by the Panel. This information will enable consumers with known allergies or intolerance to certain ingredients to select products with increased confidence of safe use.

9. One comment suggested that the Panel's indication in § 353.50(b)(1)(i) for oral wound cleansers, "For temporary use in the cleansing of wounds caused by minor oral irritation or injury such as following minor dental procedures, or from dentures or orthodontic appliances," was intended to read "For temporary use in the cleansing of minor wounds caused by oral irritation * * *." The comment also stated that the following truthful claims could be made for oral wound cleansers and oral wound healing agents based on language not recommended by the Panel but contained in or referenced in its report: "cleanses wounds caused by trauma, minor dental procedures, and other irritations of the oral soft tissues," "assists in the removal of foreign material from small superficial oral wounds," "physically removes debris from wounds," and "aids in the healing of small superficial oral wounds."

The agency believes that the Panel intended to convey to consumers the message that OTC oral wound cleanser products should be used for self-medication to cleanse minor wounds resulting from dental work, dentures, or orthodontic appliances. To reflect this intention, the agency is placing the word "minor" before the word "wounds" in the revised indication for oral wound cleansers in this tentative final monograph. Likewise, the agency is revising the Panel's definitions of "oral wound cleanser" and "oral wound healing agent" in § 353.3 (c) and (d) to reflect their use in minor oral wounds.

The comment's suggested phrase "cleanses wounds caused by traum, minor dental procedures, and other irritations of the oral soft tissues" is ambiguous. The terms "trauma" and "oral soft tissues" lack precise meaning for most consumers. The agency believes that the terms "accidental injury" and "irritations of the mouth and gums" will be more readily understood by consumers than the terms "trauma" and "irritations of the oral soft tissues." The term "minor dental procedures" was recommended by both the Panel and the comment. With minor revisions, the claim suggested by the comment would result in an indication statement that is very similar to the indication recommended by the Panel, but more meaningful to consumers. In addition, the agency is proposing that the term "minor gum inflammation" be classified as Category I and is including it in this indication. (See comment 13 below.) Therefore, the agency is proposing to revise the Panel's recommended indication as follows: "For temporary use in cleansing minor wounds or gum inflammation resulting from minor dental procedures, dentures, orthodontic appliance, accidental injury, or other irritations of the mouth and gums."

The agency believes that the statements "assists in the removal of foreign material from small superficial oral wounds" and "physically removes debris from wounds" are consistent with the labeling information the Panel intended to convey and that these statements, with light modifications to ensure accurate reflection of the agency's and the Panel's positions on labeling of OTC oral mucosal injury drug products, will provide the consumer with meaningful information on the use of oral wound cleansers. A new section (§353.50(b)(3)) entiled "Other allowable statements" is being proposed in this tentative final monograph. The statements "assists in the removal of foreign material from minor oral wounds" and "physically removes debris from minor oral wounds" are included in this section and may be used in the labeling of oral wound cleanser drug products in addition to the required indication, provided such statements are neither placed in direct conjunction with information required to appear in the labeling nor occupy labeling space with greater prominence or conspicuousness than the required information.

The phrase "aids in the healing of minor oral wounds" is not included in (§353.50(b) in this tentative final monograph. The Panel classified all oral wound healing agents in Category III (44 FR 63284 to 63287). Because no comments were received on this issue, the agency is accepting the Panel's classification and is not proposing any indications for oral wound healing agents in this tentative final monograph.

10. Two comments urged that the terms "oral discomfort," "relief of minor discomfort of minor wounds," and "soothing relief of minor wounds," be allowed in the labeling of oral wound cleansers such as carbamide peroxide in anhydrous glycerin. The comments stated that oral wound cleansers may contribute to the relief of oral discomfort due to a lesion through their cleaning and debriding action.

The Panel stated that oral mucosal injury drug products differ pharmacotherapeutically from other dental care agents, such as agents for relief or oral discomfort, in that they have no direct effect on oral discomfort, e.g., they have no anesthetic, analgesic, or protective effect (44 FR 63280). The Panel felt that these products may only indirectly provide relief of discomfort, are intended to act directly either as a cleanser or wound healing agent, and do no relieve the pain that may be associated with oral wounds. Therefore, the Panel classified the term "oral discomfort" in Category II when associated with oral mucosal injury drug products (44 FR 63284). In a separate report on drug products for the relief of oral discomfort, published in the **Federal Register** of May 25, 1982 (47 FR 22711), the Panel stated that drug products for the relief of oral discomfort are intended to act directly in terms of their specific pharmacotherapeutic properties, e.q., as local anesthetics.

The agency agrees with the Panel that labeling indications and claims for oral wound cleansers, such as "soothing" and "for relief of oral discomfort," are as yet unsupported by scientific data or evidence. The agency believes that cleansing a painful wound does not necessarily relieve the pain, and the comments did not submit data to substantiate such claims for oral mucosal injury active ingredients. However, the agency will consider reclassification of the claims "for relief of oral discomfort" and "soothing" to Category I for oral mucosal injury drug

products if adequate data are submitted to substantiate claims that an ingredient's cleansing action is "soothing" or provides "relief of oral discomfort." Because the Panel stated that oral mucosal injury drug products may indirectly provide relief of discomfort, the agency reclassifies these term from Category II to Category III in this document.

11. Two comments disagreed with the Panel's recommendations regarding "canker sores" and urged that canker sores be allowed as an indication in the Category I labeling of oral wound cleansers. The comments emphasized that canker sores are self-limiting, and that the consumer is unlikely to be adversely affected by self-treating canker sores because of the Panel's 7-day limitation of use if no improvement occurs. One comment added that canker sores tend to recur in the same persons and once diagnosed professionally (or recognized) are amenable to self-diagnosis and self-treatment by such persons. The other comment suggested the following indication: "For temporary use in the cleansing of canker sore lesions when this condition has been diagnosed by a physician."

The agency has received conflicting recommendations regarding canker sores. The Dental Panel indicated that the term "canker sore" is vague to the consumer and that canker sores cannot be self-diagnosed. The Advisory Review Panel on OTC Miscellaneous Internal Drug Products addressed the self-treatment of canker sores with orally ingested agents and defined canker sores as aphthous stomatitis, aphthous ulcers, and sores which occur on the mucous membranes of the oral cavity (often the movable areas) characterized by small whitish ulcerative lesions surrounded by a red border (see the **Federal Register** of January 5, 1982 (47 FR 504)). The Miscellaneous Internal Panel concluded that canker sores may be self-diagnosable, but are not amenable to self-treatment because their cause cannot be determined by the consumer (47 FR 505). The agency believes that, while the cause of canker sores may not be determinable by a consumer, topically applied oral wound cleansers could provide a useful function by removing debris that might become lodged in the ulcerated tissue of a canker sore. The 7-day limitation of use placed by the Dental Panel on topically applied oral wound cleansers would alert the consumer to consult a dentist or doctor if the condition for which the oral wound cleanser was used did not improve. The term canker sores has been used in the labeling of marketed products for many years. The agency believes that consumers have a general understanding of the term. Therefore, the agency proposes the following indication for oral wound cleansers (§ 353.50(b)(1)(ii)) in this tentative final monograph: "For temporary use to cleanse canker sores."

12. One comment disagreed with the Panel's placing the term "an aid to regular oral hygiene" in Category II. The comment did not object to the Panel's concern about the use of this term in the labeling of oral wound cleanser drug products, but was concerned that the term could not be used in the labeling of other products containing the same active ingredient used in an oral wound cleanser drug product but labeled for a different indication or for cosmetic use. As an example, the comment cited use of such products as an aid to regular oral hygiene by cleaning or orthodontic appliances and requested that reference to the term "an aid to regular oral hygiene" be deleted as a Category II claim for oral wound cleansing drug products.

The Panel's Category II designation of the term "an aid to regular oral hygiene" applies only to ingredients used as oral wound cleansers and not to be same ingredients used for other indications. At a later date, another panel, the Advisory Review Panel on OTC Oral Cavity Drug Products, discussed the term "oral hygiene" in its report on oral health care drug products and evaluated the ingredients in oral wound cleanser drug products for other uses in the mouth (see the **Federal Register** of May 25, 1982 (47 FR 22760)). Therefore, the agency is not classifying the term "oral hygiene" in this tentative final monograph. Use of the term "oral hygiene" in oral health care drug product labeling and any oral health care indications for active ingredients that are also oral wound cleansers will be discussed in the tentative final monograph for OTC oral health care drug products, to be published in a future issue of the **Federal Register.**

13. One comment urged that the term "minor gum inflammation" be reclassified from Category II to Category I in the labeling of both oral wound cleansers and oral wound healing agents. The comment contended that the term does not necessarily indicate the presence of bacterially caused gingivitis or periodontal disease, which the Panel viewed as serious conditions requiring treatment and supervision by a dentist or doctor (44 FR 63284). The comment suggested that "gum inflammation" may, instead, be due to toothbrush or "prophylaxic" abrasion, tooth extraction, minor surgical procedures, or orthodontia and urged that the term "minor gum inflammation" be reclassified in Category I, especially since the Panel proposed a warning against using these products for more than 7 days.

The agency agrees with the comment. The term "gum inflammation" when used alone could be interpreted by consumers as a serious condition. However, the Panel defined the term "minor gum disorders (injury)" as "inflammation related to mechanical irritation or minor injury of the gingival tissues" (44 FR 63273) and used this term to describe the type of conditions that the comment is urging be denoted as "gum inflammation" in the labeling of oral wound cleansers and wound healing agents. The agency believes that the term "minor gum inflammation" when associated with labeling describing dental procedures, dentures, orthodontic appliances, or accidental injury as the cause of the inflammation is an appropriate indication for oral wound cleansing agents. The warning proposed in § 353.50(c), which limits OTC use of oral mucosal injury drug products to 7 days, instructs the consumer to seek professional advice if the symptoms persist, do not improve, or become worse, or if swelling or fever develops. (See comment 17 below.)

Therefore, the agency is proposing that the term "minor gum inflammation" when associated with conditions such as minor dental procedures, dentures, orthodontic appliances, or accidental injury be classified in Category I. The agency is proposing the following indication for oral wound cleanser drug products in this tentative final monograph: "For temporary use in cleansing minor wounds or minor gum inflammation resulting from minor dental procedures, dentures, orthodontic appliances, accidental injury, or other irritations of the mouth and gums" (see comment 9 above). Because there are no Category I oral wound healing agents included in this tentative final monograph, no indications for these products are being proposed in this tentative final monograph.

14. One comment objected to the Panel's Category III classification of the term "oxygenating" for oral wound healing agents (44 FR 63287). The comment argued that this term is not necessarily related to tissue oxygen content when qualified by additional statements such as to "flush out food particles that ordinary brushing can miss" or to "clean and debride damaged tissue so natural wound healing can occur." The comment requested that

terms such as "oxygen rich foam" or "oxygen containing" be allowed in the labeling of oral wound healing agents to describe the mechanism by which the product works.

The OTC drug review program establishes conditions under which OTC drugs are generally recognized as safe and effective and not misbranded. Two principal conditions examined during the review are allowable ingredients and allowable labeling. The FDA has determined that it is not practical—in term of time, resources, and other considerations—to set standards for all labeling found in OTC drug products. Accordingly, OTC drug monographs regulate only labeling related in a significant way to the safe and effective use of covered products by lay persons. OTC drug monographs establish allowable labeling for the following items: 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 believes terms such as "oxygen rich foam" and "oxygen containing" are product specific and are only peripherally related to the safe and effective use of OTC oral mucosal injury drug products. Accordingly, the terms "oxygen rich foam" and "oxygen containing" are outside the scope of the OTC drug review. The agency emphasizes that these claims are, however, subject to the prohibitions in section 502 of the act (21 U.S.C. 352) relating to labeling that is false and misleading. Such terms will be evaluated in conjunction with normal enforcement activities relating to that section of the act. Moreover, any term that is outside the scope of the review, even though it is truthful and not misleading, may not appear in any portion of the labeling required by the monograph and may not detract from such rquired information.

15. One comment, from the Chairman of the Dental Panel, stated that the Panel's report needed clarification at 44 FR 63274 and 63283 to reflect that the Panel considered antimicrobial drug products which have antigingivitis claims or imply an antigingivitis claim through control of plaque (antiplaque) to be Category II at the time that the Panel completed its report, but that the Panel did not consider antiplaque agents in a thorough enough manner to allow placement in Category II and deferred evaluation of antiplaque ingredients and labeling claims to the Oral Cavity Panel. Another comment agreed with the Panel's recommendation, stating that "there is no currently available agent for plaque control or gingivitis prevention which could be placed in Category I."

The agency concurs with the Panel Chairman's clarification. The Panel deferred the evaluation of antimicrobial antiplaque ingredients and labeling claims to the Oral Cavity Panel. Antiplaque claims were discussed in that Panel's "minority report on antimicrobial agents" in the advance notice of proposed rulemaking on OTC oral health care drug products, which was published in the **Federal Register** of May 25, 1982 (47 FR 22893). The agency will address antiplaque ingredients and labeling claims, and their relationship to the prevention of gingivitis, in the tentative final monograph for oral health care drug products, to be published in a future issue of the **Federal Register.**

16. One comment pointed out that the Dental Panel (44 FR 63280) deferred consideration of antiseptic and antimicrobial claims to the Oral Cavity Drug Products Panel, which considered such claims only for the oral cavity and not for the gums or gingival tissue. The comment urged that antiseptic claims for minor injuries of the gum be specifically addressed in this tentative final monograph because such claims were not discussed in any panel's report.

In its report, the Dental Panel discussed drug products marketed for treatment of minor oral injuries but did not specifically address antiseptic claims. The Panel deferred consideration of ingredients having antiseptic claims to the Oral Cavity Panel (44 FR 63280). That Panel reviewed data for many antimicrobial agents, including the deferred ingredients, and discussed topical use of these drugs for the indications of sore mouth and sore throat, but did not specifically address antiseptic claims for minor injuries of the oral cavity, gum, or gingival tissue (47 FR 22760). FDA finds no difference between antisepsis of minor injuries of the gum or gingival tissue and other areas of the oral cavity. Therefore, the agency believes that all topical antiseptic ingredients and claims pertaining to the treatment of minor injuries of the oral cavity, including the mucous membranes of the mouth and throat, the gums, and the gingiva, can be most effectively addressed as a single topic in the tentative final monograph for oral health care drug products, to be published in a future issue of the **Federal Register.** Antiseptic claims for oral mucosal injury drug products are not addressed in this tentative final monograph.

17. Three comments suggested additions to the following warning recommended by the Panel for oral mucosal injury drug products in § 353.50(c)(1)(i): "Not to be used for a period exceeding 7 days." One of the comments endorsed the warning, but suggested that it include a statement that patients consult their dentist or physician if the condition persists beyond 7 days, adding that the patient should do something positive in addition to merely discontinung use of the product. Another of the comments stated that these products should not be limited to a specific time period if there is improvement in the condition during their use and suggested that the warning be reworded to be similar to the following: "If symptoms do not improve in seven days or if inflammation, fever or infection develops, discontinue use and see your dentist or physician."

The Panel's rationale for limiting use of OTC Oral mucosal injury drug products to 7 days was its belief that a lack of improvement of an apparent oral mucosal injury may indicate the presence of a serious condition, e.g., cancer or periodontal disease; that continued use of the product might delay diagnosis and treatment of such a condition; and that the available scientific evidence indicates that there are no indications that warrant the use of any oral mucosal injury drug product beyond 7 days except under the advice of a dentist or doctor (44 FR 63282). The agency concurs with the Panel's recommendation to limit OTC use to 7 days, but recognizes that treatment with an OTC oral mucosal injury drug product of a condition that has improved over a 7-day period should not necessarily be discontinued. However, treatment beyond 7 days should be under the care of a dentist or doctor.

The Panel recommended two warnings for oral mucosal injury drug products, "Not to be used for a period exceeding 7 days" and "Discontinue use and see your dentist or physician promptly if irritation persists, inflammation develops, or if fever and infection develop" (44 FR 63289). The Agency is proposing that these warnings be combined for clarity and stated in terms more readily understood by consumers in the following warning under § 353.50(c), which, the agency believes, meets the concerns expressed by the comments: "Do not use this product for more than 7 days unless directed by a dentist or doctor. If symptoms do not improve in 7 days; if irritation, pain, or redness persists or worsens; or if swelling or fever develops, see your dentist or doctor promptly."

E. Comments on Testing Guidelines

18. Two comments addressed the testing guidelines recommended to move an oral wound healing agent from Category III to Category I, suggesting that animal oral mucosal models other than the beagle dog indicated by the Panel should be acceptable, that models other than collagen synthesis may be useful in measuring the rate of wound healing, that data may be obtained from skin models in which only epidermal tissue is removed, and that data should be obtained by evaluating the activity of a drug in wound repair models which provide information pertinent to indications. The comments stressed that testing guidelines should be recommendations but not requirements because other tests may be available or designed which are more appropriate for testing agents for the indication or oral wound healing.

The agency agrees that the tests recommended by the Panel should be recommendations rather than requirements. Also, the Panel's guidelines do not preclude the use of any advances or improved methodology in the future (44 FR 63287). In fact, the Panel stated that "* * * industry and FDA are encouraged to develop other models to measure wound healing effectiveness * * *" (44 FR 63288).

The agency has not addressed specific testing guidelines in this document and offers the Category III testing guidelines as the Panel's recommendations without adopting them or making any formal comment on them. In revising the OTC drug review procedures relating to Category III, published in the **Federal Register** of September 29, 1981 (46 FR 47730), the agency advised that tentative final monographs will not include recommended testing guidelines for conditions that industry wishes to upgrade to monograph status. Instead, the agency will meet with industry representatives at their request to discuss testing protocols. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any oral mucosal injury drug product ingredient as well as testing protocals. (See part II. paragraph A.2. below—Testing of Category II and Category III conditions.)

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

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

1. *Summary of ingredient categories.* The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and has made the following change in the categorization of oral mucosal injury active ingredients proposed by the Panel. The agency is proposing to reclassify sodium perborate monohydrate, used as an oral wound cleanser, in Category I instead of Category II as recommended by the Panel. As a convenience to the reader, the following list is included as a summary of the categorization of oral mucosal injury active ingredients proposed by the Panel and the agency.

Oral mucosal injury active ingredients	Panel	FDA
1. Oral Wound Cleansers:		
Carbamide peroxide in anhydrous glycerin	I	I
Hydrogen peroxide in aqueous solution	I	I
Sodium perborate monohydrate	II	I
2. Oral Wound Healing Agents:		
Allantoin	III	III
Carbamide peroxide in anhydrous glycerin	III	III
Chlorophyllins, water soluble	III	III
Hydrogen peroxide in aqueous solution	III	III

2. *Testing of Category II and Category III conditions.* The Panel recommended testing guidelines for oral mucosal injury drug products (44 FR 63287). The agency is offering these guidelines as the Panel's recommendations without adopting them or making any formal comment on them. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any oral mucosal injury ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the **Federal Register** of September 29, 1981 (46 FR 47740). This policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Changes

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

1. The agency is reclassifying sodium perborate monohydrate, used as an oral wound cleanser, from Category II to Category I. New data submitted to FDA, along with data originally submitted to the Panel, support the safe and effective use of sodium perborate monohydrate as an oral wound cleanser. (See comment 4 above.)

2. The agency is proposing that the Panel's recommended indications for oral would cleanser drug products be revised in this tentative final monograph to read as follows: "For temporary use in cleansing minor wounds or minor gum inflammation resulting from minor dental procedures, dentures, orthodontic applicances, accidental injury, or other irritations of the mouth and gums." (See comments 9 and 13 above.)

3. The agency is proposing to move the indication found in § 353.50(b)(1)(ii) of the advance notice of proposed rulemaking, "For temporary use in the cleansing of gum irritation due to erupting teeth (teething)," to a new section in the tentative final monograph entitled "Professional labeling." Because the directions for oral wound cleansers specify supervised use in children under 12 years of age and prohibit use in children under 2 years of age except upon the recommendation of a dentist or doctor, the use of those ingredients for teething is contraindicated except under the supervision of a dentist or doctor. In addition, the agency is proposing that this indication for use for teething not be permitted as labeling for products containing sodium perborate monohydrate because boron is more toxic to children than to adults. (See comment 4 above.)

4. The agency is proposing to add the following indication for oral wound cleansers to § 353.50(b)(1) in this tentative final monograph: "For temporary use to cleanse canker sores." (See comment 11 above.)

5. The agency is proposing a new section (§ 353.50(b)(3)) in this tentative final monograph entitled "Other allowable statements" to include the following statements: "Assists in the removal of foreign material from minor oral wounds" and "Physically removes debris from minor oral wounds." (See comment 9 above.)

6. The agency is reclassfying the terms "soothing" and "for relief of oral discomfort" from Category II to Category III in this tentative final monograph. The agency will consider reclassification of these terms to Category I in the final monograph if adequate data are submitted to substantiate claims that an ingredient's cleansing action is "soothing" or provides "relief of oral discomfort." (See comment 10 above.)

7. The agency is proposing to combine the two warning statements in § 353.50(c)(1) (i) and (ii) of the advance notice of proposed rulemaking. The revised warning, found in § 353.50(c) in

this tentative final monograph, reads as follows: "Do not use this product for more than 7 days unless directed by a dentist or doctor. If symptoms do not improve in 7 days; if irritation, pain, or redness persists or worsens; or if swelling or fever develops, see your dentist or doctor promptly." (See comment 17 above.)

8. The agency is proposing to expand the labeling of carbamide peroxide as an oral wound cleanser by providing directions for use as an oral rinse in § 353.50(d)(1) of this tentative final monograph. (See comment 6 above.)

9. The agency is revising the definition of oral mucosal injury agent in § 353.3(b) of this tentative final monograph to be more consistent with the indications for oral mucosal injury drug products.

10. The agency is redesignating proposed Subpart D of the monograph as Subpart C and is placing the labeling sections under Subpart C.

11. In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs 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 other applicable OTC drug regulations will give manufacturers the option of using either the word "physician" or the word "doctor." This tentative final monograph proposes that option.

The agency proposes to revoke the existing caution statement in § 369.20 for sodium perborate (sodium perborate monohydrate) mouthwash, gargle, and toothpaste at the time that the monographs for oral mucosal injury drug products, oral cavity drug products, and anticaries drug products become effective.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the Federal Register of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule for OTC oral mucosal injury 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 or small entities. However, this particular rulemaking for OTC oral mucosal injury drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

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

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

List of Subjects in 21 CFR part 353

OTC drugs; Oral mucosal injury drug products.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11, it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended by adding new Part 353, to read as follows:

PART 353—ORAL MUCOSAL INJURY PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Subpart B—Active Ingredients

Subpart C—Labeling

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

Subpart A—General Provisions

§ 353.1 Scope.

(a) An over-the-counter oral mucosal injury 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 part and each of the general conditions established in § 330.1.

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

§ 353.3 Definitions.

As used in this part:

(a) *Oral mucosal injury.* Injury occurring to the soft tissue in the oral cavity.

(b) *Oral mucosal injury agent.* An agent that relieves oral soft tissue injury by cleansing or promoting the healing of minor oral wounds or irritations.

(c) *Oral wound cleanser.* A nonirritating preparation that assists (physically or chemically) in the removal of foreign material from minor oral wounds and does not delay wound healing.

(d) *Oral wound healing agent.* A nonirritating agent that aids in the healing of minor oral wounds by means other than cleansing and irrigating, or by serving as a protectant.

Subpart B—Active Ingredients

§ 353.10 Oral mucosal injury active ingredients.

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

(a) *Oral wound cleansers.*

(1) Carbamide peroxide 10 percent in anhydrous glycerin.

(2) Hydrogen peroxide 3 percent in aqueous solution.

(3) Sodium perborate monohydrate 1.2 gram dry powder to be dissolved in 30 milliliters of water.

(b) *Oral wound healing agents.* [Reserved]

§ 353.20 Permitted combinations of active ingredients.

(a) Any single oral wound healing agent identified in § 353.10(a) may be combined with any single generally recognized as safe and effective oral antiseptic.

(b) Any single oral wound cleanser identified in § 353.10(b) may be combined with any single generally recognized as safe and effective oral antiseptic.

(c) Any single oral wound healing agent identified in § 353.10(b) may be combined with a denture adhesive.

Subpart C—Labeling

§ 353.50 Labeling of oral mucosal injury drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug(s), if any, and identifies the product as either an "oral wound cleanser" or an "oral wound healing agent."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to one or more of the following phrases:

(1) *For oral wound cleanser drug products.*

(i) "For temporary use in cleansing minor wounds or minor gum inflammation resulting from minor dental procedures, dentures, orthodontic appliances, accidental injury, or other irritations of the mouth and gums."

(ii) "For temporary use to cleanse canker sores."

(2) *For oral wound healing agent drug products.* [Reserved]

(3) *Other allowable statements.* In addition to the required information specified in paragraphs (a), (b) (1) and (2), (c), and (d) of this section, the labeling of the product may contain any of the following statements, provided such statements are neither placed in direct conjunction with information required to appear in the labeling nor occupy labeling space with greater prominence or conspicuousness than the required information.

(i) "Assists in the removal of foreign material from minor oral wounds."

(ii) "Physically removes debris from minor oral wounds."

(c) *Warnings.* The labeling of the product contains the following warning under the heading "Warnings": *For products containing any ingredient identified in § 353.10 (a) and (b):* "Do not use this product for more than 7 days unless directed by a dentist or doctor. If symptoms do not improve in 7 days; if irritation, pain, or redness persists or worsens; or if swelling or fever develops, see your dentist or doctor promptly."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions."

(1) *For products containing carbamide peroxide identified in § 353.10(a)(1)*—(i) *For direct application.* Apply several drops directly to the affected area of the mouth. Allow the medication to remain in place at least 1 minute and then spit out. Use up to four times daily after meals and at bedtime or as directed by a dentist or doctor. Children under 12 years of age should be supervised in the use of this product. Children under 2 years of age: consult a dentist or doctor.

(ii) *For use as an oral rinse.* Place 10 to 20 drops onto tongue. Mix with saliva. Swish around in the mouth over the affected area for at least 1 minute and then spit out. Use up to four times daily after meals and at bedtime, or as directed by a dentist or doctor. Children under 12 years of age should be supervised in the use of this product. Children under 2 years of age: consult a dentist or doctor.

(2) *For products containing hydrogen peroxide identified in § 353.10(a)(2)*—(i) *For direct application.* Apply several drops of full strength (3 percent) solution to the affected area of the mouth. Allow the medication to remain in place at least 1 minute and then spit out. Use up to four times daily after meals and at bedtime or as directed by a dentist or doctor. Children under 12 years of age should be supervised in the use of this product. Children under 2 years of age: Consult a dentist or doctor.

(ii) *For use as an oral rinse.* Mix the full strength (3 percent) solution with an equal amount of warm water. Swish around in the mouth over the affected areas for a least 1 minute and then spit out. Use up to four times daily after meals and at bedtime or as directed by a dentist or doctor. Children under 12 years of age should be supervised in the use of the product. Children under 2 years of age: consult a dentist or doctor.

(3) *For products containing sodium perborate monohydrate identified in § 353.10(a)(3) for use as an oral rinse.* Dissolve 1.2 grams of sodium perborate monohydrate in 1 ounce (30 milliliters) of warm water. Use immediately. Swish solution around in the mouth over the affected area for at least 1 minute and then spit out. Do not swallow. Use up to four times daily after meals and at bedtime or as directed by a dentist or doctor. Children under 12 years of age should be supervised in the use of this product. Children under 6 years of age: consult a dentist or doctor.

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

§ 353.60 Professional labeling.

The labeling of products containing carbamide peroxide identified in § 353.10(a)(1) and hydrogen peroxide identified in § 353.10(a)(2) provided to health professionals (but not to the general public) may contain the following indication: "For temporary use in the cleansing of gum irritation due to erupting teeth (teething.)"

Interested persons may, on or before September 26, 1983, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before November 23, 1983. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announed in the **Federal Register.**

Interested persons, on or before July 26, 1984, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classifed in Category I. Written comments on the new data may be submitted on or before September 26, 1984. These dates are consistent with the time periods specified in the

agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA-305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on September 26, 1984. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register**, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Dated: July 8, 1983.

Mark Novitch,

Acting Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

[FR Doc. 83-20088 Filed 7-25-83; 8:45 am]

BILLING CODE 4160-01-M