DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201, 356, and 369

[Docket No. 81N-0033]

Oral Health Care Drug Products for Over-the-Counter Human Use; Tentative Final Monograph

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) oral health care anesthetic/analgesic, astringent, debriding agent/oral wound cleanser, and demulcent drug products (products for use in the mouth and throat) are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the reports and recommendations of the Advisory Review Panel on OTC Oral Cavity Drug Products and the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products, public comments to the advance notices of proposed rulemaking on OTC oral health care drug products and OTC oral mucosal injury drug products that were based on the respective Panels' recommendations, and public comments on the agency's proposed regulation on OTC oral mucosal injury drug product, which was issued in the form of a tentative final monograph. This proposal incorporates part of the tentative final monograph on OTC oral mucosal injury drug products that was published in the **Federal Register** of July 26, 1983 (48 FR 33984) into the rulemaking for OTC oral health care drug products and 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 Drugs by May 26, 1988. Because of the length and complexity of this proposed regulation, the agency is allowing a period of 120 days for comments and objections instead of the normal 60 days. New data by January 27, 1989. Comments on the new data by March 27, 1989. Written comments on the agency's economic impact determination by May 26, 1988.

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, Center for Drug Evaluation and Research (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of May 25, 1982 (47 FR 22760), 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 health care drug products, together with the recommendations of the Advisory Review Panel on OTC Oral Cavity Drug Products (Oral Cavity Panel), 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 August 23, 1982. Reply comments in response to comments filed in the initial comment period could be submitted by September 22, 1982. In a notice published in the **Federal Register** of July 30, 1982 (47 FR 32953), FDA extended the periods for comments and reply comments to allow more time for interested persons to adequately address several important issues raised by the Panel. The notice extended the comment period to November 22, 1982 and the reply comment period to December 22, 1982. In a notice published in the **Federal Register** of December 28, 1982 (47 FR 57739), FDA extended the reply comment period to January 21, 1983 to allow time for interested persons to adequately address several important issues raised during the comment period.

In response to the advance notice of proposed rulemaking, fifteen drug manufacturers, three professional organizations, four health professionals, and two individual consumers submitted comments.

Because there is considerable overlap between the rulemaking on OTC oral mucosal injury drug products and the rulemaking on OTC oral health care drug products, the agency is incorporating that part of the oral mucosal injury rulemaking that covers oral wound cleansers into this tentative final monograph. The 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. 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 it in this tentative final monograph. Oral wound healing agents, also addressed in the tentative final monograph for OTC oral mucosal injury drug products, were addressed in a final rule published in the **Federal Register** of July 18, 1986 (51 FR 26112).

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 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.

The agency received no written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs in response to the tentative final monograph on OTC oral mucosal injury drug products.

In accordance with § 330.10(a)(10), the data and information considered by the Panels and the agency are on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above). Copies of the comments received are also on public display in the Dockets Management Branch.

FDA is issuing the tentative final monograph for OTC oral health care drug products in several segments. This document is the first segment to be published, and it contains the agency's responses to general comments on OTC oral health care drug products and to comments on OTC oral health care anesthetic/analgesic, astringent, debriding agent/oral wound cleanser, and demulcent drug products. A subsequent segment of the tentative final monograph on OTC oral health care drug products will be published in a future issue of the **Federal Register** and will contain the agency's responses to

comments regarding oral health care antimicrobial drug products, and comments on the drug or cosmetic status of certain oral health care ingredients and claims.

In order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10), the present document is designated as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule) to establish Part 356 (21 CFR Part 356), FDA states for the first time its position on the establishment of a monograph for OTC oral health care (anesthetic/analgesic, a stringent, debriding agent/oral wound cleanser, and demulcent) drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph for these drug products.

This proposal constitutes FDA's tentative adoption of the Oral Cavity Panel's conclusions and recommendations on these drug products, as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report, and the agency's reevaluation of the previously published proposed rule on OTC oral mucosal injury drug products. 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) now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA 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 product that is subject to the monograph 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 application. Further, any OTC drug product subject to this monograph that is repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In the advance notice of proposed rulemaking for OTC oral health care drug products (published in the **Federal Register** of May 25, 1982 (47 FR 22760)), the agency suggested that the conditions included in the monograph (Category I) be effective 6 months after the date of publication of the final monograph in the **Federal Register.** 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 6 months 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 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 reformulate their products and have them in compliance in the marketplace.

If the agency determines that any labeling for a condition included in the final monograph should be implemented sooner than the 12-month effective date, 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 July 20, 1973 (38 FR 19444) 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 Health Care Drug Products

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

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

2. Noting its continued opposition to the exclusivity policy, one comment stated that FDA should not prohibit the use of alternative OTC labeling

terminology to describe indications, if that terminology is truthful, not misleading, and intelligible to the consumer. The comment's views on this subject were presented in oral and written testimony submitted to FDA in connection with the September 29, 1982 FDA hearing on the exclusivity policy.

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

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

3. One comment suggested that the phrase "Try to avoid swallowing this product" be deleted as a warning for oral health care gargles, mouthwashes, and rinses because the "Warnings" section on the label should be reserved for instances that pose a serious threat to the well-being of the consumer. The comment contended that the Panel's recommended warning is unduly alarming to consumers who may conclude that swallowing even a minute quantity of the product will result in substantial harm. The comment suggested that reference to the fact that the product is not intended to be swallowed be included in the "Directions" section of the label rather than in the "Warnings" section. The comment then claimed that the phrase "Expel remainder" more clearly signifies the proper and intended use of these products without unnecessarily alarming consumers. The comment gave the following example: "Rinse thoroughly and expel remainder."

The agency agrees with the comment that information regarding swallowing or not swallowing an oral health care liquid dosage form is more appropriately included in the directions section than in the warnings section of the label. Including this information in the directions section is consistent with the style and format of other recently published OTC tentative final monographs.

The agency is not including the Panel's recommended warning in §§ 356.50(c)(3), 356.52(c)(2), 356.54(c)(2), and 356.56(c)(2), "Try to avoid swallowing this product," in this tentative final monograph. Instead, along with other modifications (see comments 10, 11, 27, and the Summary of the Agency's Changes, Nos. 18 and 19, below), the agency is proposing the phrase "and then spit out" as part of the directions in this tentative final monograph (e.g., "Gargle, swish around in the mouth, or allow to remain in place for at least 1 minute, and then spit out"). Including the phrase "and then spit out" points out that such products are not intended to be swallowed and is consistent with the working for directions already proposed by the agency for liquid dosage forms in the tentative final monograph for OTC oral mucosal injury drug products (48 FR 33993). The agency did not receive any comments opposed to this proposal. The agency believes that the phrase "spit out" is better understood by the consumer and is preferable to the comment's suggested phrase "expel remainder."

B. General Comments on Anesthetic/Analgesic Drug Products

4. One comment stated that topical anesthetic/analgesic drug products are often promoted to the public with claims or implications that they prevent or treat diseases of the mouth or upper respiratory tract. Objecting to the OTC use of these drug products for the relief of pain or other symptoms of oral disease, the comment stated that the need to use topical anesthetic/analgesic drug products should be ascertained by a dentist or a physician. In addition, the comment said that OTC use of these drug products "may delay patients seeking professional care for the underlying disease."

A reply comment disagreed with the comment's position, stating that it "is a denial of the public's right to self-medicate for conditions that can be safely and effectively managed utilizing over-the-counter drugs appropriately labeled."

The agency agrees that these products should not be labeled to prevent or treat diseases, but disagrees with the comment that a health professional should first be consulted. The agency agrees with the reply comment regarding OTC use of topical anesthetic/analgesic drug products for oral health care. The Panel recommended labeling indications that clearly state that these products are to be used for the temporary relief of occasional minor irritation, pain, sore mouth, and sore throat. The Panel also provided warnings to discontinue use and to consult a physician if irritation persists or increases or if a rash appears on the skin and to consult a physician promptly for symptoms such as a severe or persistent sore throat or a sore throat accompanied by high fever, headache, nausea, and vomiting, which may indicate a serious condition. There are also warnings not to use a product indicated for sore throat for more than 2 days and not to use a product indicated for sore mouth for more than 7 days unless directed by a doctor.

The agency believes that the indications and warnings proposed in this tentative final monograph provide adequate labeling for the safe and effective OTC use of these products. Therefore, topical anesthetic/analgesic ingredients are included in this tentative final monograph.

5. One comment noted that the Panel's recommended monograph did not provide for professional labeling for anesthetic/analgesic agents. The comment stated that the agency has long recognized the need for labeling OTC drugs directed exclusively to health care professionals because physicians frequently prescribe nonprescription products for the treatment of various conditions. The comment added that under Category II labeling for anesthetics/analgesics (47 FR 22826), the

Panel included a list of phrases as indications for use in conditions that properly require diagnosis by a physician. These indications include relief of pain associated with such conditions as tonsilitis, pharyngitis, and throat infections and such terms as "stomatitis" and "aphthous ulcers."

The comment agreed with the Panel that these conditions require professional diagnosis, but pointed out that Category I anesthetic/analgesic products are safe and effective for use in such instances. Therefore, the comment requested that the above indications for OTC oral health care products containing anesthetic/analgesic ingredients be included under § 356.85 *professional labeling,* for dissemination to health care professionals (but not to the general public).

The Panel placed OTC label claims that referred to pharyngitis, tonsilitis, and aphthous ulcers in Category II to guard against self-diagnosis and self-treatment of conditions that are not amenable to OTC treatment (47 FR 22785). The agency agrees with the Panel that such claims are not appropriate for OTC labeling. However, the agency believes that Category I OTC anesthetic/analgesic ingredients are as effective in relieving the pain associated with conditions that must be diagnosed by a physician as they are in relieving the occasional minor irritation, pain, sore throat, and sore mouth that can be self-diagnosed. Moreover, in its discussion on sore mouth, the Panel stated that anesthetic/analgesic ingredients can be used as adjuncts to therapeutic regimens outlined by physicians in conditions where professional care is necessary (47 FR 22776). At the present time, there are some OTC anesthetic/analgesic drug products on the market that are also promoted to health care professionals for some of the indications that were placed in Category II by the Panel (Refs. 1 and 2). The agency has determined that OTC anesthetic/analgesic drug products can be used for the relief of pain associated with tonsilitis, pharyngitis, and throat infections which must first be diagnosed by a physician. Therefore, professional labeling is being included in the tentative final monograph to alert health care professionals to the additional indications. In a new section, § 356.80, the agency is proposing that the professional labeling of products containing anesthetic/analgesic ingredients, identified in § 356.10, may contain the following indication: "For the temporary relief of pain associated with" (select one or more of the following conditions: "tonsilitis," "pharyngitis," "throat infections," or "stomatitis") However, these same indications remain in Category II for use on the labeling of these OTC drug products marketed directly to consumers because consumers cannot self-diagnose and self-treat these conditions.

Regarding the condition of "aphthous ulcers" (canker sores) mentioned by the comment, the agency has determined that this condition is self-diagnosable and self-treatable. Accordingly, as explained in comment 6 below, the agency is including in § 356.55 for anesthetic/analgesic ingredients the OTC indication "For temporary relief of pain associated with canker sores."

References

(1) "Physician's Desk Reference For Nonprescription Drugs," 7th Edition, Medical Economics Company, Oradell, NJ, p. 650, 1986.

(2) OTC Volume 130038.

6. One comment objected to the Panel's Category II classification of the indication "For temporary relief of pain associated with canker sores." The comment stated that canker sores are oral mucosal lesions that are commonly and accurately diagnosed by the consumer. The comment added that canker sores are usually self-limiting and seldom lead to complications, and that it is not in the best interest of the consumer to require that professional advice be sought prior to treatment with local anesthetics that have been proven safe and effective. The comment requested that the agency modify § 356.50(b) to include the indication "For temporary relief of pain associated with canker sores."

The agency agrees with the comment and believes that canker sores can be recognized by the consumer and that the pain associated with canker sores is amenable to treatment with OTC anesthetic/analgesic active ingredients. The agency notes that the Advisory Review Panel on OTC Miscellaneous Internal Drug Products concluded that canker sores are self-limiting, tend to reoccur in the same individual, are self-diagnosable, but are not amenable to self-treatment because of their diverse and usually unknown etiology (47 FR 504 to 505). However, in the tentative final monograph for OTC oral mucosal injury drug products (48 FR 33984), the agency stated that oral wound cleansing agents may be labeled for temporary use in cleansing canker sores because those agents could provide a useful function by removing debris from the ulcerated tissue. The agency believes that OTC anesthetic/analgesic active ingredients may provide an additional useful function by alleviating the pain commonly associated with canker sores. Therefore, in this tentative final monograph, the agency is proposing to modify § 356.55(b) to include the following indication for oral health care anesthetic/analgesic active ingredients: "For temporary relief of pain associated with canker sores."

7. One comment pointed out that statements referring to the time of onset of action of local anesthetics applied to the mucous membranes, in terms other than in definite units of time, were placed in Category II by the Panel (47 FR 22826). The comment stated that for all local anesthetics/analgesics included in the Panel's recommended monograph, the onset of activity is virtually instantaneous, occurring within seconds. The comment also stated that this rapid onset of action is the basis for the rational use of anesthetics in local pain relief and that the inclusion of such terms as "fast" or "quick" in reference to onset of action for these agents is truthful and not misleading. The comment contended that such terms are properly considered as product attributes and that the agency should not prohibit communication of these qualities to the consumer.

Claims concerning characteristics of product performance or attributes will be dealt with in OTC drug monographs only when they imply the existence of a characteristic that would be therapeutically significant for the drug in question. For example, "rapid onset" is a property that is not necessarily significant for most OTC drugs, including topical oral anesthetic/analgesic agents, but is important to the effective use of a bronchodilator in counteracting an asthma attack. Because the claims "fast" or "quick" are not directly related to the safe and effective use of topically applied oral anesthetic/analgesic agents, the agency considers these claims to be outside the scope of the monograph. The agency will continue to evaluate these claims, on a product-by-product basis, under the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 352) relating to labeling that is false and misleading. Any term that is outside the scope of the monograph, even though it is truthful and not misleading, may not appear on any portion of the labeling that is required by the monograph and may not detract from the required information. However, such terms may be included on the labeling provided that they are not intermixed with labeling established by

the monograph, and the statement is not false or misleading.

8. One comment disagreed with the Panel's recommended dosage of benzocaine as an anesthetic/analgesic for use in a throat lozenge. The Panel recommended a dosage of 2 to 15 milligrams (mg) benzocaine in the form of a lozenge every 2 hours, if necessary. The comment proposed that the upper limit of benzocaine for adult use be increased to a maximum of 40 mg every half hour, as necessary, with a maximum adult dosage of 1.3 grams (g) of benzocaine per day.

The comment based its recommendation on marketing experience, feedback from customers, and taste tests. The comment stated that taste tests, conducted on company personnel, showed that a dose of 20 mg benzocaine is necessary to produce an effective level of anesthesia in the throat when sugar-based lozenges are used and that in sugar-free products, the anesthetic effect appears to be inhibited and a larger dose of benzocaine (up to 40 mg) is needed. The comment added that at these doses, the duration of anesthesia in the throat is approximately 30 minutes. The comment also stated that its stability studies show that in a warm, moist environment, similar to that encountered in the throat, benzocaine is rapidly degraded; thus, a dosage interval of every 30 minutes rather than every 2 hours is more appropriate. Citing the "United States Dispensatory" and the Panel's discussion of toxicity data on benzocaine (47 FR 22808 to 22809), the comment emphasized that its recommended dosage does not produce harmful or toxic effects from benzocaine or its degradation products (i.e., ethanol and *p*-aminobenzoic acid).

Because the comment did not submit any clinical data to support an increase in the maximum dosage of benzocaine in a lozenge formulation, the undocumented statements made by the comment cannot be considered adequate proof of the safety and effectiveness of a 20-mg or 40-mg dose of benzocaine as a lozenge to be used every 30 minutes. Therefore, the agency cannot accept the higher dosage recommended by the comment for this ingredient without additional data being provided to support such a change.

9. One comment requested that the agency consider phenol and phenolate sodium, at a total concentration of 0.5 to 1.5 percent expressed as phenol, as a single active ingredient rather than as a combination in drug products. The comment pointed out that the Dental Panel, in its report on OTC drug products for the relief of oral discomfort, considered phenol and phenolate sodium to be a single active ingredient (47 FR 22712). The comment also noted that the Advisory Review Panel on Antimicrobial (II) Drug Products (Antimicrobial II Panel), in its report on OTC topical antifungal drug products, stated that it considered phenol and phenolate sodium to be a single active ingredient when both are contained in a product formulation and that the total level of phenol and phenolate sodium is expressed as percent phenol. (See the **Federal Register** of March 23, 1982; 47 FR 12480.)

According to the comment, in many rulemaking proceedings the agency "has considered salts of active ingredients synonymous with the free acid or base when such salts do not significantly change the safety or efficacy of that free acid or base." The comment further objected to these products being subject to the combination sections of the monograph and pointed out that phenolate sodium invariably arises from phenol-containing formulations when pH adjustments are required to make such products pharmaceutically acceptable, and not for the purpose of combining two distinct active ingredients.

The agency has reviewed the Dental Panel's report on OTC drug products for the relief of oral discomfort and finds that the Panel evaluated several drug products containing phenol and phenolate sodium (47 FR 22739). However, the Panel did not distinguish between phenolate sodium and phenol as separate single ingredients or classify such drug products as combinations. It considered such drug products as single active ingredient products containing phenol as the active ingredient.

The agency has also reviewed the Antimicrobial II Panel's report on topical antifungal drug products and notes that the Panel discussed phenol and phenolate sodium in a single writeup and discussed safety and effectiveness based on the concentration of phenol (47 FR 12517).

The Oral Cavity Panel recognized that the active moiety in phenolate sodium is phenol, and recommended for a liquid dosage form a concentration of 0.5 to 1.5 percent for phenol as a single ingredient and a concentration equivalent to 0.5 to 1.5 percent phenol for phenolate sodium as a single ingredient. For a solid dosage form, the Panel recommended 10 to 50 mg of phenol as a single ingredient and a concentration equivalent to 10 to 50 mg phenol for phenolate sodium as a single ingredient (47 FR 22814 to 22816).

The agency concludes that, because safety and effectiveness as an anesthetic/analgesic is based on the concentration of phenol, products containing both phenolate sodium and phenol are not considered as drug products containing two separate single active ingredients and are not combination drug products subject to the combination requirements in § 356.20 of the monograph. Accordingly, phenol identified in § 356.10(g) and phenolate sodium identified in § 356.10(h) of the Panel's recommended monograph are replaced in proposed § 356.10 of this tentative final monograph with the following: "(f) Phenol preparations (phenol and/or phenolate sodium)."

10. One comment stated that the Oral Cavity Panel had unnecessarily restricted the dosing frequency for phenol and phenolate sodium liquid formulations (mouthwashes, gargles, liquids, and sprays) in § 356.50(d) (7) and (8) of its recommended monograph. The comment stated that a number of studies submitted to the agency indicate that 2 hours is the maximum duration of effective anesthesia/analgesia typically induced by these ingredients. Thus, the Panel's recommended maximum frequency of "three to four times daily" is too restrictive. In addition, the comment contended that this dosing frequency is inconsistent with the dosing frequency for lozenges, which is every 2 hours. The comment requested that the dosing frequency for phenol and phenolate sodium liquid preparations be revised to every 2 hours.

The agency agrees with the comment that the data support a dosing frequency of every 2 hours for phenol-containing liquid formulations rather than three to four times daily as recommended by the Panel. Several of the studies submitted to the agency indicate that the duration of relief afforded by aqueous solutions of 1.5 percent phenol ranges from 30 minutes or less to approximately 2 hours (Refs. 1 through 4). Only one study (Ref. 3) mentioned a number of subjects (17 out of 44) who experienced relief defined as lasting longer than 2 hours. In that study, 27 subjects reported relief lasting 1 hour or less. Although these studies were submitted to the Panel, they were not discussed in the Panel's evaluation of this ingredient.

The agency believes that the use of 0.5 to 1.5 percent phenol-containing liquid formulations at a dosage frequency of every 2 hours is safe. In its report on OTC drug products for the relief of oral discomfort (47 FR 22712), the Dental Panel recommended that the daily dosage of phenol not exceed 600 mg daily for adults and 300 mg daily for children 6 to 12 years of age (47 FR 22759). When an aqueous solution of

phenol is used according to label directions as a mouthwash or gargle, the amount of phenol absorbed or ingested is small and well below the maximum daily dosage recommended by the Dental Panel. One study (Ref. 5) demonstrates that when 1 fluid ounce of a 1.4-percent phenol solution (411 mg phenol) is used as a gargle or mouthwash with a rinse time of 2 minutes before spitting out, approximately 50 mg phenol (12 percent) is retained or absorbed in the oral cavity. The recommended rinse time for phenol-containing mouthwashes or gargles is 15 seconds (Refs. 1 and 6) indicating that under conditions of normal use, less than 12 percent of the phenol in the dose is retained or absorbed in the oral cavity after a single application of the drug product. Even if an adult applied 25 milliliters (mL) of a drug product containing 1.5 percent phenol every 2 hours with a rinse time of 2 minutes before spitting out, less than 550 mg of phenol would be absorbed or retained in the oral cavity over a 24-hour period, and the recommended maximum daily adult dosage of 600 mg phenol would not be exceeded.

Because there is an adequate margin of safety when label directions are followed and because the duration of anesthesia induced by phenol-containing drug products is less than 2 hours, the agency concludes that the maximum dosing frequency of phenol-containing liquid dosage forms should be every 2 hours, the same as the dosing frequency of phenol-containing lozenges (solid dosage forms). Therefore, in § 356.55(d)(6) of this tentative final monograph, the agency is proposing revised directions for products containing phenol preparations (phenol and/or phenolate sodium) that reflect a dosing frequency of every 2 hours.

References

(1) Bronsky, D.A., "to Evaluate the Efficacy of Both Chloraseptic Solution and Chloraseptic Lozenges When Used to Relieve the Gingival and Buccal Mucosal Discomfort Associated with Orthodontic Braces," draft of unpublished study, C00014, Docket No. 80N-0033, Dockets Management Branch.

(2) Blum, B., "Clinical Evaluation of an Anesthetic Mouthwash," *The New York State Dental Journal*, 26:419-421, 1960.

(3) Young, J.R., "Use of Phenol Anesthetic Spray for Pain Relief," *E.E.N.T. Digest*, 30:51-60, 1968.

(4) Braunlin, E.A., "Evaluation of an Antiseptic, Anesthetic Solution," *Journal of the National Medical Association*, 56:151-152, 1964.

(5) OTC Volume 130065

(6) OTC Volume 13ATFM.

11. One comment noted that although the Panel's recommended monograph provides for a gel form of benzocaine as an anesthetic/analgesic, a gel formulation for phenol was apparently inadvertently omitted. The comment requested that phenol as a 0.5- to 1.5-percent gel (i.e., the Category I concentration of phenol as an anesthetic/analgesic ingredient in a gel formulation) be included in the tentative final monograph.

The agency agrees that an aqueous gel formulation is an acceptable dosage form of phenol for use as an anesthetic/analgesic. Moreover, any Category I oral health care active ingredient may be formulated in any rational dosage form that is consistent with the directions for use of the product, provided that the ingredient is present at the specified dosage and the product is manufactured according to the regulations for the Current Good Manufacturing Practice for Finished Pharmaceuticals (21 CFR Part 211). Therefore, the agency finds it unnecessary to list specific dosage forms for oral health care drug products unless the dosage form is specifically relevant to the use, safety, or effectiveness of the ingredient.

Accordingly, to allow for the different solid dosage forms (e.g., lozenges, compressed tablets) and nonsolid dosage forms (e.g., mouthwashes, gels) that may be used when formulating oral health care drug products, the agency is using the terms "solid dosage forms" and "dosage forms other than solid" in this tentative final monograph and is not adopting words such as "rinse," "mouthwash," "lozenge," "gel," etc., that appeared in the advance notice of proposed rulemaking, except where the specific dosage form is relevant to the use, safety, or effectiveness of the ingredient. The directions in §§ 356.55(d), 356.65(d), 356.70(d), and 356.75(d) of this tentative final monograph, where appropriate, use the terms "solid dosage forms" and "dosage forms other than solid."

12. Although agreeing with the Panel's recommended concentration of 0.04 to 2 percent menthol as an anesthetic/analgesic in liquid oral health care products (47 FR 22928), one comment contended that the recommended dosage for menthol per lozenge (2 to 20 mg) does not include the lowest dosage level that was submitted to the Panel. The comment claimed that a submission to the Panel contained a study showing that 1 mg menthol per 2-g lozenge exerted a statistically significant pharmacologic effect in the oral cavity (Ref. 1). The comment contended that as a result of reviewing the study in the submission to the Panel (Ref. 1) and subsequent literature provided on the method used in the study (Ref. 2), the Panel accepted the citric acid aerosol test for the assessment of drug activity. The comment recommended revision of the minimum effective dose for menthol in lozenges to include doses down to and including 1 mg per lozenge.

The agency reviewed the submission referred to by the comment (Ref. 1), but did not find a study using a concentration of 1 mg menthol per 2-g lozenge. The only study in the submission that specified the concentration of menthol was one in which menthol was used in combination at a concentration of 9 mg per 3-g lozenges (Ref. 3). The agency concludes that the data in this study cannot be used to support the effectiveness of menthol as an oral health care anesthetic/analgesic ingredient at doses down to and including 1 mg per lozenge, as recommended by the comment, because the study investigated a higher dose of menthol in a combination product. Therefore, any pharmacologic effect observed in the oral cavity can neither be attributed to menthol alone nor to menthol at the lower dosage level, as the comment claims.

Regarding the comment's statement that the Panel accepted the citric acid aerosol test for the assessment of drug activity, the agency's position, as stated in the **Federal Register** of October 19, 1983 (48 FR 48582), is that induced-cough studies are supportive, but are not a substitute for adequate and well-controlled studies in the target population. Additionally, cough reduction alone is not sufficient proof of the effectiveness of an ingredient labeled as an anesthetic/analgesic for oral health care use. Studies conducted on drugs for these uses must demonstrate a decrease in sore mouth or sore throat pain.

Therefore, the agency is proposing a Category III classification for less than 2 mg menthol as an anesthetic/analgesic active ingredient for use in a solid dosage form.

References

(1) OTC Volume 130095.

(2) Packman, E.W., and S.J. London, "The Utility of Artificially Induced Cough as a Clinical Model for Evaluating Antitussive Drug Combinations. Part I: Liquid and Solid Formulations of Systemic Drug," *Current Therapeutic Research*, 21:855-866, 1977.

(3) Packman, E.W., "Victors" (Study CRD No. 71-7), draft of unpublished study, OTC Volume 130095.

13. One comment noted that the Panel recommended a 0.05 to 5 percent concentration of benzyl alcohol as an anesthetic/analgesic ingredient as a liquid and a minimum of 100 mg as a lozenge. The comment stated that for a

usual 2-g lozenge, 100 mg corresponds to 5 percent, the maximum concentration allowed for liquids. However, because a lozenge is in contact with the oral cavity for a much longer period of time than a mouthwash or a spray, the benzyl alcohol has a much greater opportunity to exert the desired effect. Noting that as little as a 1-percent concentration is used for parenteral injection to produce an anesthetic effect, the comment recommended that the minimum content of benzyl alcohol for use in a lozenge be reduced to 5 mg (equivalent to 0.05 percent in 10 mL of a solution).

The Panel recommended a maximum concentration of 10 percent benzyl alcohol when formulated as a liquid, not 5 percent as stated by the comment (47 FR 22928). Thus, the amount of benzyl alcohol in the 2-g lozenge containing 100 mg of benzyl alcohol mentioned by the comment would not correspond to the maximum concentration recommended for a liquid.

The Panel acknowledged that the effect of benzyl alcohol when incorporated in a lozenge is sustained as long as the mucous membranes are bathed in a sufficient concentration of drug, but that the duration of action when benzyl alcohol is incorporated in rinses is brief, seldom more than 5 to 10 minutes (47 FR 22810). It would be expected that lower concentrations, such as 1 percent benzyl alcohol, when injected parenterally or when used as a rinse would produce an anesthetic effect because all of the drug is immediately available. In lozenge form, however, the amount of drug available is dependent upon other factors, such as the dissolution rate of the lozenge and the total concentration of drug in the lozenge. Thus, the anesthetic effect of the two formulations (lozenge and liquid) containing the same concentration of benzyl alcohol may not be the same because the amount of benzyl alcohol available at any one time in a lozenge would be less than that available in a liquid.

The Panel believed that a minimum dose of 100 mg in a lozenge is appropriate in order to produce an anesthetic effect. No data were submitted by the comment to support the effectiveness of a dose lower than 100 mg per lozenge for benzyl alcohol as a topical anesthetic/analgesic active ingredient. Therefore, the agency has no basis for proposing that 5 mg be the minimum allowable content for a lozenge. The agency invites the submission of data in support of the effectiveness of the comment's suggested lower minimum dose for benzyl alcohol in lozenge form.

14. Urging approval of internal analgesics for relief of minor sore throat pain, two comments stated that internal analgesics have been properly used for many years to treat this minor condition. The comments provided several references to support this claim. The comments pointed out, however, that the Advisory Review Panel on Over-the-Counter (OTC) Internal Analgesic and Antirheumatic Products (Internal Analgesic Panel) placed such claims for internal analgesics in Category II. The comments disagreed with the recommendation, noting that the review of drugs for relief of minor sore throat pain was assigned to the Oral Cavity Panel. Therefore, the comments considered it appropriate to include internal analgesics for this indication in the monograph for OTC oral health care drug products.

The agency notes that the Oral Cavity Panel was charged with evaluating ingredients and labeling used in OTC anesthetic/analgesic preparations intended strictly for local, topical application to the mucous membranes of the oral cavity (mouth) and pharynx (throat). The Oral Cavity Panel either classified ingredients and labeling for anesthetic/analgesic preparations that act systemically as Category II (47 FR 22765), or it deferred those ingredients known or presumed to be absorbed and to act systemically to other panels for evaluation.

The agency agrees with the Oral Cavity Panel's recommendation that systemic relief of minor sore throat pain should be addressed in the rulemaking for OTC internal analgesic, antipyretic, and antirheumatic drug products and has transferred all comments and associated submissions regarding internal analgesics for the relief of minor sore throat pain to that rulemaking (Docket No. 77N–0094) (Ref. 1). The agency's findings on this subject will be addressed within the context of the rulemaking for OTC internal analgesic, antipyretic, and antirheumatic drug products in a future issue of the **Federal Register**. The agency discusses the use of topically applied aspirin for the relief of minor sore throat pain in this tentative final monograph. (See comment 15 below.)

Reference

(1) Memo No. 00006, Docket No. 77N–0094, Dockets Management Branch.

15. Two comments agreed with the Panel's majority report on the safety and effectiveness of aspirin that "aspirin is safe and effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat * * *." (47 FR 22796). One comment concurred with the majority of the Panel that the speed of the response excluded a systemic analgesic effect resulting from the absorption of aspirin. Both comments stated that these conclusions were based on a careful review of the published literature, the submissions to the Panel, and the original, independent work of one of the Panel members.

One comment maintained that several of the safety issues raised in the Panel's minority report on aspirin as a topical analgesic were not unique to aspirin in chewing gum form and were not supported by the quoted references. The comment then listed the following examples:

(1) The effect of a conventional aspirin tablet applied directly to the mucous membranes of the mouth (47 FR 22799) has little relevance to the evaluation of the safety of aspirin in chewing gum form.

(2) One of the reports of mouth ulcers associated with aspirin in chewing gum form cited in the minority report (47 FR 22799) involved an obvious abuse situation in which the consumer had chewed 8 to 10 gum tablets a day for 6 to 10 weeks.

(3) Two references to several cases of massive hemorrhage from the tonsillar bed following topical application of a "gargle of aspirin-containing chewing gum" (47 FR 22800) have been incorrectly quoted. The comment stated that neither reference involves the topical application of a "gargle of aspirin containing chewing gum." It asserted that one of these references presented the results of laboratory experiments in dogs treated with a variety of substances, including aspirin, placed in the gastrointestinal tract. The other reference discusses the effect of an aspirin suspension intended for systemic absorption.

(4) The comment quoted the following statements from the Panel's minority report (47 FR 22800): "Hemorrhage was observed in 8 percent of 100 posttonsillectomy patients medicated with aspirin * * *. No bleeding occurred in 100 patients medicated with acetaminophen." The comment stated that this report involved an aspirin suspension and therefore was not applicable to aspirin in chewing gum form.

(5) A study cited in the Panel's minority report (47 FR 22800) described a high incidence of post-tonsillectomy bleeding in children treated with an aspirin-containing chewing gum. The comment stated that this study involved a select subgroup of the population, and that it would be more sensible to restrict

the use of aspirin-containing gum by this small subgroup than to deny the rest of the population the benefit of such a product. The comment maintained that the warnings included in § 356.50(c)(2)(iv) of the Panel's recommended monograph prohibit the use of chewable aspirin-containing drug products immediately following oral surgery.

The comment maintained that the safety concerns voiced by the minority of the Panel were not adequately documented and that some concerns would be more properly handled by labeling than by removal of the product. The comment requested that aspirin in a chewing gum dosage form remain in Category I for safety as a topical analgesic consistent with the conclusion of the majority of the Panel.

The majority of the Panel concluded that aspirin incorporated in a chewing gum base is safe and effective as an OTC anesthetic/analgesic ingredient for topical use on the mucous membranes of the mouth and throat. However, the minority of the Panel members concluded that there were insufficient data available to permit final classification of the safety and effectiveness of aspirin as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat. The minority of the Panel members had serious reservations about the safety of topically applied aspirin used in the oral cavity and believed that aspirin has no known topical anesthetic or analgesic activity. They felt that any analgesic effect from aspirin applied topically in the oral cavity is ultimately due to systemic absorption and not to topical application.

In the tentative final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products, to be published in a future issue of the **Federal Register**, the agency will discuss the systemic effectiveness of aspirin in chewing gum form for the relief of many kinds of pain including sore throat pain. However, with regard to the effectiveness of aspirin as a topical analgesic active ingredient for use on the mucous membranes of the mouth and throat, the agency disagrees with the comments and agrees with the minority of the Oral Cavity Panel members that there are insufficient data available to permit final classification.

The conclusion of the majority of the Panel members that aspirin is an effective topical analgesic ingredient was based upon a Panel member's oral presentation to the Panel describing his independent research, which was later published in the literature (Ref. 1), and upon a study by Scott (Ref. 2) indicating that aspirin applied topically to dentin in artificial cavities in a cat's incisor inhibits steady state discharge and response to a brief heat stimulus. However, the agency believes that aspirin's mode (or modes) of action have not been well elucidated and another recent publication by Adriani, Minokadeh, and Naraghi (Ref. 3), which was not available to the Panel, contradicts the results of the Panel member's research mentioned above (Ref. 1). This more recent study used an established method of algesimetry in which an electric current is applied to the tip of the tongue as a painful stimulus and found that a saturated solution of aspirin has no more analgesic effect on the tip of the tongue than the placebo (saline).

In the advance notice of proposed rulemaking for OTC external analgesic drug products (published in the **Federal Register** of December 4, 1979; 44 FR 69846 to 69847), the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products (Topical Analgesic Panel) stated that aspirin possesses no topical anesthetic activity and does not block the neuronal membranes as do topical anesthetics such as benzocaine. That Panel concluded that although percutaneous absorption of salicylate occurs, any subsequent analgesic effect is systemic and not local. In the advance notice of proposed rulemaking for OTC internal analgesic, antipyretic, and antirheumatic drug products (published in the **Federal Register** of July 8, 1977; 42 FR 35376 to 35377), the Internal Analgesic Panel determined that although aspirin has historically been used as a gargle for the treatment of minor sore throat pain, aspirin or any analgesic in a gum base has not been adequately tested for effectiveness in the treatment of sore throat pain. That Panel deferred aspirin in a chewing gum base and the use of aspirin as a gargle for a local topical effect to the Oral Cavity Panel for evaluation (42 FR 35376 and 47 FR 22801). Although the topical use of aspirin in chewing gum dosage form for the relief of minor sore throat pain is discussed in this notice, the agency has determined that the role of internal analgesic drug products, including the systemic effects of aspirin in a chewing gum form, and their labeling for the relief of minor sore throat pain will be addressed within the context of the rulemaking for OTC internal analgesic drug products in a future issue of the **Federal Register**. (See comment 14 above.)

The agency believes that because there was a divided recommendation by the Oral Cavity Panel, because two other Panels concluded that aspirin has no known local analgesic effect, and because the referenced publications (Refs. 1 and 3) present conflicting data, a reasonable question exists regarding the ability of aspirin to exert a topical analgesic effect on the oral mucosa. Furthermore, it should be noted that the agency is not aware of any OTC aspirin products in tablet or lozenge dosage form that are marketed specifically for topical use. The OTC aspirin product in a chewing gum dosage form that was submitted to the Internal Analgesic Panel as an internal analgesic and subsequently was submitted to the Oral Cavity Panel is not specifically labeled for topical oral use. The product's current indications include temporary relief of minor sore throat pain, headache, aches and pains of colds, and muscular aches and pains (Ref. 4). Therefore, the agency is classifying aspirin when labeled for topical use in Category III for effectiveness as an analgesic for use in the oral cavity for the relief of pain associated with minor sore throat. The agency recommends that testing using protocols similar to those employed in the study by Adriani, Minokaden, and Naraghi (Ref. 3) are necessary to demonstrate that aspirin produces a statistically and clinically significant topical analgesic effect in the oral cavity. Manufacturers may want to discuss their proposed protocol(s) with the agency prior to performing studies. The agency invites further comments and data on this use of aspirin.

With regard to the safety of aspirin for topical use in the oral cavity, the agency accepts the conclusion of the majority of the Panel and agrees with the comments that aspirin in a chewing gum base is safe for topical use on the mucous membranes of the mouth and throat when labeled with adequate warnings against misuse. The agency also agrees with the one comment that two references (Refs. 5 and 6) cited in the Panel's minority report (47 FR 22800) are misquoted. However, both articles do point out that aspirin is irritating to mucous membranes and emphasize the need for proper labeling.

Also, contrary to the comment's contention, two publications (Refs. 7 and 8) cited in the minority report (47 FR 22799) did involve aspirin in a chewing gum base. In one case report, aspirin in a chewing gum and aspirin tablets were both applied to the roof of the mouth and resulted in local ulceration within a week. Upon removal of both forms of medication, the ulceration healed (Ref.

7). In this report, the lesions could have been caused by either form of aspirin or the unusual combination of both. In the other case report, a consumer chewed 8 to 10 gum tablets a day for 6 to 10 weeks (Ref. 8). Although prolonging treatment with aspirin-containing chewing gum for 6 to 10 weeks is an abusive situation, the ulcers were reported to have been present for 6 to 10 weeks also. This indicates that the ulcers could have been caused by or aggravated by misuse of the aspirin-containing chewing gum. The ulcers healed promptly when the gum was discontinued. These two reports, as well as another mentioned by the comment (Ref. 9), indicate the topical irritant action of salicylates on the mucous membranes of the mouth and point out the necessity for adequate warnings against misuse.

The agency acknowledges that aspirin increases bleeding time and inhibits platelet aggregation (42 FR 35384 and 47 FR 22797). In addition, aspirin-related hemorrhage after oral surgery is a well-documented occurrence (Refs. 10, 11, and 12). The agency agrees with both the Panel and the one comment that aspirin in any form should not be used after oral surgery or tonsillectomy (47 FR 22798 and 22801). In addition, the agency agrees with the Panel that aspirin should not be used either systemically or topically when mucous membranes are highly inflamed or abraded, when there are eroded, bleeding lesions, or when the consumer is on anticoagulant medication (47 FR 22798). In order to address the above-mentioned safety concerns, the majority of the Panel suggested the following warnings for aspirin-containing oral health care drug products in its recommended monograph:

Section 356.60(c)(2)(ii) "Do not use if you have a bleeding problem or if you are taking an anticoagulant drug."

Section 356.60(c)(2)(iii) "Do not use without a physician's or dentist's advice if your mouth is highly irritated or ulcerated."

Section 356.60(c)(2)(iv) "Do not use after surgery in the mouth or throat."

The agency believes that these warnings, with some minor modifications, are sufficient to protect the consumer against any adverse effects resulting from the use of aspirin in a chewing gum base in the oral cavity. The Internal Analgesic Panel, in its report, recommended that all aspirin products formulated to be chewed before swallowing (chewable tablets or gums) should contain the following warning: "Do not take this product for at least 7 days after tonsillectomy or oral surgery except under the advice and supervision of a physician" (47 FR 35385). The agency believes that prohibiting the use of aspirin for 7 days after oral surgery is reasonable and is recommending this as a required warning.

The agency also believes that the recommended warnings can be shortened by combining them into a single statement and that the phrase "except under the advice and supervision of a dentist or doctor" should be added to the combined warning. In addition, the agency believes that consumers may not understand the meaning of the word "anticoagulant." In the tentative final monograph for OTC internal analgesic drug products, to be published in a future issue of the **Federal Register**, the agency plans to explain the word "anticoagulation" by placing the words "thinning the blood" in parentheses after it. The same approach is being recommended in this tentative final monograph also.

The agency is recommending that the following warning be included in the final monograph for OTC oral health care drug products if aspirin in a chewing gum base becomes a Category I ingredient in this rulemaking:

> Do not use if you have a bleeding problem, if you are taking a prescription drug for anticoagulation (thinning the blood), if your mouth is highly irritated or ulcerated, or for at least 7 days after surgery in the mouth or throat except under the advice and supervision of a dentist or doctor.

In conclusion, in this tentative final monograph, the agency is classifying aspirin in a chewing gum base in Category III for effectiveness and in Category I for safety as a topical anesthetic/analgesic active ingredient for use in the oral cavity. If this ingredient is included in the final monograph for OTC oral health care drug products, the agency will consider the need for any additional warnings that are required for aspirin in the final monograph for OTC internal analgesic drug products.

References

(1) Loch, W.E.E., et al., "Local Aspirin Analgesia in the Oral Cavity," *Clinical Pharmacology and Therapeutics*, 33:642–648, 1983.

(2) Scott, D., Jr., "Aspirin: Action on Receptor in the Tooth," *Science*, 161:180–181, 1968.

(3) Adriani, J., S. Minokadeh, and M. Naraghi, "Effectiveness on Mucous Membranes of Topically Applied Antipyretic Analgesics," *Regional Anesthesia*, 6:47–50, 1981.

(4) OTC Volume 13ATFM.

(5) Davenport, H.W., "Gastric Mucosal Injury by Fatty and Acetylsalicylic Acids," *Gastroenterology*, 46:245–253, 1964.

(6) Reuter, S.H., and W.W. Montgomery, "Aspirin vs. Acetaminophen after Tonsillectomy: A Comparative Double-Blind Study," *Archives of Otolaryngology*, 80:214–217, 1964.

(7) Kawashima, Z., R.H. Flagg, and D.E. Cox, "Aspirin-Induced Oral Lesion: Report of Case," *Journal of the American Dental Association*, 91:130–131, 1975.

(8) Claman, H.N., "Mouth Ulcers Associated with Prolonged Chewing of Gum Containing Aspirin," *Journal of the American Medical Association*, 202:651–652, 1967.

(9) Roth, I.L.A., et al., "Topical Action of Salicylates in Gastrointestinal Erosion and Hemorrhage," *Gastroenterology*, 44:146–158, 1963.

(10) Singer, R., "Acetylsalicylic Acid, A Probable Cause for Secondary Post-Tonsillectomy Hemorrhage," *Archives of Otolaryngology*, 42:19–20, 1945.

(11) Hersh, R. A., "A Clinical Study Comparing the Incidence of Postoperative Bleeding in Patients Using Salicylate-containing Analgesics versus Acetaminophen Analgesics," *Bulletin of the Bergen County Dental Society*, 40:6–8 and 16, 1974.

(12) Fox, S. L., and C. B. West, "Vitamin K and Late Tonsillar Hemorrhage," *Laryngoscope*, 51:564–574, 1947.

16. One comment requested that the agency revise the Category I dosage schedule for topical aspirin as follows:

Adults—325–500 mg every 4 hours as needed not to exceed 3,900 mg in 24 hours.

Children 9 to 11—200–500 mg every 4 hours as needed, not to exceed 2,030 mg in 24 hours.

Children 6 to 8—130–325 mg every 4 hours as needed, not to exceed 1,625 mg in 24 hours.

The comment maintained that most of the efficacy and safety data and experience submitted to the Panel for evaluation was based upon a formulation containing 227 mg aspirin per gum tablet and that this concentration is not included in the Panel's recommended dosage schedule. The comment stated that the proposed revision takes into account the actual Category I dosage range (130 to 500 mg) officially approved by the Panel at its December 14, 1979 meeting, provides an age-dependent dosage as proposed in the Panel's majority report on aspirin, and provides a Category I dosage range that includes the currently available products.

The agency believes that a specific dosage schedule for topically applied aspirin in a chewing gum base cannot be proposed at this time because of the absence of actual study data to support such a dosage schedule. Although the comment proposes doses as low as 130 mg aspirin, no data were submitted to the Panel or the agency that would support the topical analgesic

effectiveness of such a low dose of aspirin. As the comment stated, most of the information submitted to the Panel for evaluation (Ref. 1) was derived from a product containing 227 mg aspirin per tablet in a chewing gum base. Other data submitted to the agency regarding the topical analgesic effectiveness of aspirin (Ref. 2) were based on a dose of 210 mg of aspirin, but that amount was in an aqueous solution, not a chewing gum base. Neither dose was shown to be effective.

Therefore, the agency disagrees with the Panel's Category I classification of aspirin in a chewing gum base as an oral health care topical analgesic/anesthetic drug product and is proposing a Category III classification for this ingredient. (See comment 15 above.) Consequently, the agency is not proposing a dosage schedule for this ingredient as an oral health care drug product. In the event that aspirin in a chewing gum base reaches monograph status (Category I), the agency will establish an appropriate dosage at that time, based on the supporting data.

References

(1) OTC Volume 130104.

(2) Loch, W. E. E, et al., "Local Aspirin Analgesia in the Oral Cavity," *Clinical Pharmacology and Therapeutics*, 33:642–648, 1983.

17. One comment maintained that because aspirin in a chewing gum base can be labeled for use as an internal analgesic and/or a topical analgesic, provisions should be made to allow the warnings to be consolidated. It stated that the 2-day administration restriction should be identified as applicable only when treating sore throat, and that the 5-day to 10-day restriction would be applicable to internal analgesic use.

In this document, aspirin is classified in Category III for effectiveness as a topical anesthetic/analgesic ingredient. (See comment 15 above.) However, if aspirin is included in the final monograph for OTC oral health care drug products as well as in the final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products, a product could display labeling from both monographs. For example, manufacturers may indicate on the label that the 2-day usage limitation is applicable only when treating sore throat, and that the 5-day to 10-day restriction on use applies when aspirin is used as an internal analgesic for the temporary relief of minor aches and pains such as headaches. Manufacturers may combine warnings, indications, and directions, respectively, to eliminate duplicative words or phrases so that the resulting information is clear and understandable.

18. One comment maintained that the Panel's recommended warning in § 356.50(c)(2)(v), "Provide good fluid intake when aspirin or aspirin-containing preparations are used" is unnecessary for products containing aspirin in a chewing gum form because the process of chewing generates sufficient saliva to prevent pharyngeal or esophageal irritation. The comment added that the topical effect of aspirin could be diminished by the administration of liquids immediately after chewing the gum tablets. Therefore, the comment requested that the agency delete this warning for these drug products.

In this document, aspirin is classified as Category III for effectiveness as a topical anesthetic/analgesic ingredient. (See comment 15 above.) However, the agency agrees with the comment that if aspirin in a chewing gum base is shown to have a topical analgesic effect in the oral cavity, that effect could be negated or diminished by drinking water after chewing the tablets. In addition, the agency believes that the process of chewing the aspirin-containing gum produces enough saliva to prevent any irritation the aspirin might cause in the oral cavity. Therefore, if aspirin in a chewing gum base is included as a topical anesthetic/analgesic ingredient in the final monograph for OTC oral health care drug products, the agency proposes that the warning recommended by the Panel in § 356.50(c)(2)(v) should not be required.

C. General Comments on Debriding Agent/Oral Wound Cleanser Drug Products

19. Noting that the Dental Panel and the Oral Cavity Panel reviewed some of the same ingredients (i.e., carbamide peroxide and hydrogen peroxide) used at similar concentrations at the same or adjacent sites in the oral cavity, one comment pointed out similarities between the Oral Cavity Panel's definition of a debriding agent (47 FR 22927) and the Dental Panel's definition of an oral wound cleanser (44 FR 63289). The comment stated that the removal of foreign material by debriding agents and by oral wound cleansers is accomplished by utilizing oxygen-releasing moieties whose foaming action mechanically and chemically removes devitalized tissue, mucus, phlegm, etc. The comment claimed that it is confusing and misleading to consumers when the same ingredients, used for the same therapeutic purpose at the same or adjacent sites, have different labeling. The comment requested that the definitions, warnings, and indications be consistent between the two monographs.

The agency has reviewed the definitions, warnings, and indications for debriding agents in the Oral Cavity Panel's report (47 FR 22927 to 22929) and for oral wound cleansers in the tentative final monograph for OTC oral mucosal injury drug products (48 FR 33992 to 33993). The agency agrees with the comment that there are many similarities between debriding agents and oral wound cleansers. The Dental Panel defined an oral wound cleanser as "a nonirritating preparation that assists (physically or chemically) in the removal of foreign material from minor oral wounds and does not delay wound healing" (44 FR 63289). The Oral Cavity Panel defined a debriding agent as "an agent which causes 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).

Debriding agents remove debris by either a mechanical, chemical, biochemical, or physicochemical mechanism of action, such as the release of oxygen, the lowering of pH, and by osmosis (47 FR 22905). Oral wound cleansers, generally, achieve the physical removal of debris by releasing oxygen, which results in a foaming action (44 FR 63280). The agency believes that the therapeutic effect of debriding agents and oral wound cleansers is the same, i.e., removal of foreign or devitalized materials from minor wounds or inflammations in the oral cavity.

Because of the overlap and similarities in the definitions, therapeutic effect, mechanisms of action, and site of action of oral wound cleansers and debriding agents, the agency has decided to incorporate part of the rulemaking for OTC oral mucosal injury drug products into this tentative final monograph for oral health care drug products. The tentative final monograph for OTC oral mucosal injury drug products was published in the **Federal Register** of July 26, 1983 (48 FR 33984) and proposed conditions under which OTC oral wound cleansers and oral wound healing agents would be generally recognized as safe and effective. Only oral wound cleansing ingredients and labeling are included in this segment of the oral health care tentative final monograph. The combination of an oral wound cleanser and an oral antiseptic proposed in § 353.20(b) of the tentative final monograph for OTC oral mucosal injury drug products will be addressed in the

second segment (i.e., oral health care antimicrobial drug products) of this rulemaking. Oral wound healing agents were addressed in a final rule published in the **Federal Register** of July 18, 1986 (51 FR 26112). Definitions relevant to oral wound cleansers are being proposed in § 356.3 of this tentative final monograph. Indications, warnings, and directions relevant to oral wound cleansers are incorporated into § 356.70 of this tentative final monograph, which pertains to debriding agents. The resultant class of ingredients will hereafter be identified as oral health care debriding agent/oral wound cleansers.

20. One comment stated that although it does not recognize a therapeutic benefit from the use of cleansing and debriding agents, it is generally accepted that several agents are effective at cleansing and debriding the oral mucosa. The comment agreed with the Panel's recommendations that the following agents are safe and effective for those indications: hydrogen peroxide, sodium bicarbonate, and carbamide peroxide in anhydrous glycerin.

One reply comment noted that the comment partially agreed with the Panel's findings on cleansing and debriding agents, but that the comment did not recognize the therapeutic benefit of debriding agents, as did the Panel, and that both the Oral Cavity Panel and the Dental Panel placed debriding agents in Category I. The reply comment urged the agency to maintain the Category I indications for debriding agents.

The agency agrees with the Panel's conclusion that debriding agents are drugs that provide a therapeutic benefit to the target population because they aid in the symptomatic relief of sore mouth and sore throat by removing thick, tenacious mucus, purulent secretions, and debris that may stimulate pain receptors in ulcerated or inflamed areas of the mouth and throat (47 FR 22905). Therefore, the agency is proposing Category I indications for oral health care debriding agents in this tentative final mongraph.

21. One comment agreed that the Panel's recommended drug claims are appropriate for debriding agents, but argued that these ingredients are also useful as mechanical cleansers that perform an important cosmetic function. The comment requested that debriding agents be available for use in oral hygiene products intended solely for cleansing the mouth for cosmetic purposes.

Products marketed only as cosmetics are not subject to this rulemaking. Because the final mongraph will cover only the drug use of the active ingredients listed therein, the concentration range, limitations, statements of identity, indications, warnings, and directions established for these ingredients in the monograph will not apply to the use of the same ingredients in products intended solely as cosmetics. However, if a product is intended for both drug and cosmetic use, it must conform to the requirements of the final monograph. In addition to the indications allowed for OTC oral health care drug products, such products may also bear appropriate labeling for cosmetic uses, in conformity with section 602 of the Act (21 U.S.C. 362) and the provisions of 21 CFR Parts 701 and 740.

In accordance with the final rule on the agency's "exclusivity policy" (51 FR 16258), it is the agency's view that cosmetic claims may not appear within the boxed area designated "APPROVED USES." As discussed at 51 FR 16264 (paragraph 14), cosmetic claims may appear elsewhere in the labeling but not in the box should manufacturers choose the labeling alternative provided in § 330.1(c)(2) (i) or (iii) for labeling cosmetic/drug products.

22. Two comments disagreed with the Panel's Category II classification of sodium perborate monohydrate as an oral health care debriding agent (47 FR 22908). One comment stated that the Panel did not thoroughly evaluate the available data. The other comment stated that a review of the information in the Panel's report did not justify a Category II classification for sodium perborate monohydrate from the standpoint of safety.

In the tentative final monograph for OTC oral mucosal injury drug products (48 FR 33984), the agency concluded that sodium perborate monohydrate is safe for use in the oral cavity as an oral wound cleanser if the ingredient is limited to dosage units of not more than 1.2 g (to be dissolved in 30 mL of water) and if its use in children under 6 years of age is prohibited. The agency also concluded that 1.2 g sodium perborate monohydrate releases 1.3 to 1.4 percent hydrogen peroxide (a Category I oral wound cleanser) and therefore may be considered an effective oral wound cleanser because the activity of hydrogen peroxide-containing compounds is a physical phenomenon based on the foaming action caused by the release of molecular oxygen when the compound comes into contact with tissue or saliva (48 FR 33986). The foaming action loosens and lifts out debris, thus cleansing the wound.

As stated in comment 19 above, the agency is incorporating part of the rulemaking on OTC oral mucosal injury drug products into the sections of this tentative final monograph pertaining to debriding agents. Therefore, the agency is proposing a Category I classification for sodium perborate monohydrate as a debriding agent/oral wound cleanser. The agency also concludes that the directions proposed for sodium perborate monohydrate as an oral wound cleanser are appropriate for sodium perborate monohydrate as a debriding agent/oral wound cleanser. (See § 353.50(d)(3) at 48 FR 33993.) Therefore, with minor format modifications, those directions are being proposed in this tentative final monograph.

23. One comment referred to the Oral Cavity Panel's statement that long-term, daily use of peroxides can cause gingival inflammation, tooth decalcification, and black hairy tongue (47 FR 22875). The comment maintained that the statement lacked the scientific clarification found in the report on OTC oral mucosal injury drug products (44 FR 63281), i.e., that only high concentrations (6 to 30 percent) of hydrogen peroxide may cause these adverse reactions. The comment stated that these adverse reactions are not associated with currently marketed products containing 3 percent hydrogen peroxide and 10 to 15 percent carbamide peroxide. The comment concluded that long-term safety is not at issue because debriding agents and oral wound cleansers are generally used intermittently for a week or less, and that the literature does not support a lack of safety in humans during either long-term or short-term use.

The agency notes that the Oral Cavity Panel provided a more detailed explanation of the possible adverse effects from the use of high concentrations of peroxide (6 to 30 percent) (47 FR 22875 to 22877) than the Dental Panel (44 FR 63281 to 63282). The Oral Cavity Panel discussed more studies showing adverse changes in the gingival tissue and the tongue as a result of the frequent use of hydrogen peroxide at high concentrations. The Dental Panel mentioned only a few of the studies showing adverse effects. Therefore, the agency rejects the comment's contention that the report on OTC oral mucosal injury drug products contains a clearer scientific explanation of the adverse effects of high concentration of hydrogen peroxide than the report on OTC oral health care drug products.

The Oral Cavity Panel was concerned about the chronic use of hydrogen

peroxide in such products as antimicrobial-containing mouthwashes as well as the short-term use in debriding agents. The Dental Panel was only concerned about the short-term use of hydrogen peroxide in oral wound cleansers. One reference cited by the Oral Cavity Panel stated that hydrogen peroxide should not be used as a mouthwash for long periods of time because of its acidity and because hydrogen peroxide at low concentrations can decalcify teeth (Ref. 1).

Because both Panels concluded that concentrations of hydrogen peroxide up to 3 percent are safe for short-term use only, adverse reactions resulting from the use of higher concentrations are not relevant to this segment of the oral health care rulemaking. However, possible adverse reactions resulting from the chronic use of hydrogen peroxide at low concentrations are relevant to the antimicrobial segment of the rulemaking for OTC oral health care drug products because antimicrobial-containing mouthwashes may be used for extended periods of time. Possible adverse reactions resulting from the chronic use of hydrogen peroxide as a mouthwash will be discussed in the antimicrobial segment of this rulemaking. Therefore, the agency disagrees with the comment that long-term safety is not an issue.

Reference

(1) Dobbs, E.C., "Pharmacology and Oral Therapeutics," 12th Ed., C.V. Mosby Co., St. Louis, p. 427, 1961.

24. One comment requested that the "description" of carbamide peroxide in § 356.14(a) be revised to indicate that the active ingredient is carbamide peroxide in anhydrous glycerin and that § 356.54(d)(1) be revised to agree with the Panel's description of carbamide peroxide in its discussion at 47 FR 22905. The comment explained that it is incorrect to describe carbamide peroxide as a solution in water, as in the directions in § 356.54(d)(1), because the ingredient is not available as an aqueous solution inasmuch as it degrades to urea and hydrogen peroxide when contacting water. Referring to § 356.14(a), the comment explained that carbamide peroxide alone is also incorrect because degradation occurs if carbamide peroxide is present as a single unstabilized ingredient.

The agency concludes that §§ 356.14(a) and 356.54(d)(1) of the advance notice of proposed rulemaking should be revised as requested by the comment. Because carbamide peroxide is an unstable compound that breaks down if exposed to air or water, it is stabilized by formulation in anhydrous glycerin (47 FR 22863). (Anhydrous glycerin may be prepared by heating glycerin USP at 150 °C for 2 hours to drive off the moisture content.) Therefore, in this tentative final monograph, the agency is proposing that § 356.16(a) read as follows: "Carbamide peroxide in anhydrous glycerin." In addition, because carbamide peroxide is unstable in water (44 FR 63281), and it is neither formulated in water nor used in aqueous solution, the agency is not including any reference to a solution containing carbamide peroxide in water in the directions proposed in § 356.70(d)(1) of this tentative final monograph. (See comment 27 below.)

25. One comment noted that, although the definition of a debriding agent refers to its action on unhealthy tissues (47 FR 22927), the indication for a debriding agent recommended by the Panel in § 356.54(d) (47 FR 22929) limits use only to "Aids in the removal of phlegm, mucus, or other secretions in the temporary relief of discomfort due to occasional sore throat and sore mouth." The comment suggested that the indication be expanded to include the activity noted in the definition section regarding removal of oral secretions, foreign material, and devitalized or contaminated tissue from or adjacent to a lesion or irritated tissue which can occur in sore mouth, sore throat, and sore gums.

The comment suggested that § 356.54(b) be revised by adding the following:

(1) "For temporary use in cleansing of wounds caused by minor oral irritation or injury such as following minor dental procedures or from dentures or orthodontic appliances."

(2) "For temporary use in the cleansing of gum irritation due to erupting teeth (teething)."

The first indication suggested by the comment is similar in content to the indication proposed by the agency in §353.50(b)(1)(i) of the tentative final monograph for OTC oral mucosal injury drug products (48 FR 33993). The second indication proposed by the comment is identical to the professional labeling proposed in § 353.80 of that tentative final monograph. The agency is incorporating the proposed indications and professional labeling for oral wound cleansers into §§ 356.70 and 356.80 of this tentative final monograph. (See comment 19 above.) The comment's concern has been addressed by this action.

26. One comment stated that the Oral Cavity Panel recommended that debriding agents be used no longer than 2 days without professional supervision, whereas the Dental Panel proposed that the same active ingredients, when used as oral wound cleansers, should not be used longer than 7 days without professional supervision (44 FR 63282). Adding that the 7-day use limit provided for oral wound cleansers better approximates the healing time needed to effectively repair mucous membrane irritation and lesion, the comment cited the American Dental Association's notation that mild and asymptomatic oral lesions generally require 5 to 10 days for healing (Ref. 1). The comment recommended that the 2-day limit proposed for debriding agents be revised to the 7-day limit recommended for oral wound cleansers.

The comment also noted that the Oral Cavity Panel recommended that children can use debriding agents at age 3 (47 FR 22906), whereas the Dental Panel stated that children can use oral wound cleansers at age 2 (44 FR 63281). The comment recommended the use of debriding agents by children 2 years of age and older because limited toxicity is associated with the Category I ingredients and because teething in children may necessitate the use of a "debriding agent/oral wound cleanser." The comment further stated that it is unnecessarily alarming to include the age limitations in the warnings section and recommended that reference to age be deleted from the warnings section of the labeling of debriding agents because the age limit is included in the directions.

In addition, the comment requested that the reference in § 356.54(c)(1)(ii) to a rash appearing on the skin after use of a debriding agent be deleted because the appearance of a rash is neither noted in, nor supported by, the safety reviews of any of the debriding agents.

Accordingly, the comment suggested the following warning for OTC oral health care debriding agents:

(i) If improvement is not seen after 7 days of use, discontinue use and see a physician. Severe or persistent sore throat, or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly.

The agency has decided to incorporate portions of the rulemaking for OTC oral mucosal injury drug products into this tentative final monograph and to consider debriding agents and oral wound cleansers as one therapeutic class called debriding agent/oral wound cleansers. (See comment 19 above.) In addition, because this therapeutic class of ingredients (i.e., debriding agent/oral wound cleansers) has not historically been used for the relief of sore throat symptoms and

because the therapeutic benefits of using these ingredients for sore throat symptoms are not apparent, the agency is proposing that debriding agent/oral wound cleansers be limited to use only in relieving symptoms associated with a sore mouth.

The Oral Cavity Panel recommended that all OTC oral health care drug products be used for sore throat in addition to sore mouth. Therefore, the Panel recommended the 2-day use limit for all of these products because of the risk of serious illness if appropriate treatment of a sore throat is delayed. However, in its discussion of sore mouth, the Panel stated that although sore mouth may denote the presence of a condition that requires diagnosis and treatment by a physician, in most cases it is caused by minor ulcerations and other benign conditions that are self-limited and generally heal spontaneously in 7 to 10 days (47 FR 22774 to 22776).

In the tentative final monograph for OTC oral mucosal injury drug products, the agency agreed with the Dental Panel that even though the presence of an oral lesion or inflammation can be a symptom of a serious disease, oral wound cleansers may be used for up to 7 days without consulting a physician or dentist (48 FR 33993). Because debriding agent/oral wound cleansers in this tentative final monograph are indicated only for use to relieve the symptoms associated with sore mouth, and sore mouth is unlikely to be indicative of a serious health threat, the agency is proposing that debriding agent/oral wound cleansers can be safely used to relieve the symptoms associated with sore mouth for up to 7 days before seeking professional guidance.

The agency agrees with the comment that the lowest age for use of debriding agents by children should be 2 years. These active ingredients are applied topically and are only inadvertently ingested. In general, they exhibit low toxicity (47 FR 22905). Therefore, the agency is proposing that the lower age limit for use of OTC oral health care debriding agent/oral wound cleansers except sodium perborate monohydrate (see comment 22 above) should be 2 years. In addition, the agency agrees with the comment that because the age limitations are in the directions, they are not necessary in the warning statements.

The agency believes that the comment has misinterpreted the warning statement concerning the appearance of a rash. The Oral Cavity Panel's warning statement is not meant to imply that the appearance of a rash is an adverse reaction caused by the use of a debriding agent/oral wound cleanser. Rather, the appearance of a rash may be a symptom of serious diseases, such as scarlet fever, measles, or chicken pox, which can appear after initial sore mouth symptoms and which require professional advice and supervision (47 FR 22776). Thus, reference to a rash is an appropriate part of the warning statements for debriding agent/oral wound cleansers.

The agency believes that, with minor modification, the warning proposed in § 353.50(c) of the tentative final monograph for OTC oral mucosal injury drug products is appropriate for the oral health care debriding agent/oral wound cleansers included in this tentative final monograph and that this warning can be combined with the Oral Cavity Panel's recommended warning in § 356.54(c)(1)(ii). Therefore, the agency is proposing to replace the warnings recommended by the Oral Cavity Panel in § 356.54(c)(1) with the following warning: "Do not use this product for more than 7 days unless directed by a dentist or doctor. If sore mouth symptoms do not improve in 7 days; if irritation, pain, or redness persists or worsens; or if swelling, rash, or fever develops, see your dentist or doctor promptly." This warning is proposed in § 356.70(c)(1) of this tentative final monograph.

Reference

(1) "Accepted Dental Therapeutics," 38th ed., Council on Dental Therapeutics of the American Dental Association, Chicago, p. 292, 1979.

27. One comment stated that the directions recommended by the Oral Cavity Panel for carbamide peroxide do not reflect the labeling and use of the products submitted to the agency for review. The comment suggested that the directions for carbamide peroxide as an oral wound cleanser in § 353.50(d)(1) of the Dental Panel's recommended monograph for OTC oral mucosal injury drug products would, if modified to include use as a rinse in addition to use by direct application, be appropriate for carbamide peroxide as a debriding agent. The comment requested that the agency revise the directions for carbamide peroxide as a debriding agent and make the directions for debriding agents in this tentative final monograph consistent with the directions for oral wound cleansers in the recommended monograph for OTC oral mucosal injury drug products.

As discussed in comment 19 above, the agency is incorporating portions of the tentative final monograph for OTC oral mucosal injury drug products into this mongraph. The agency believes that, with minor format changes, the directions it proposed for carbamide peroxide and hydrogen peroxide as oral wound cleansers (48 FR 33993) are also appropriate for those ingredients when used as debriding agent/oral wound cleansers. The agency also believes that these directions reflect the labeling and use of products submitted to the agency for review. Therefore, with minor format changes, the directions proposed in § 353.50(d)(1) and (2) of the tentative final monograph for OTC oral mucosal injury drug products are being proposed in this tentative final monograph.

D. General Comments on Decongestant and Expectorant Drug Products

28. One comment maintained that the Oral Cavity Panel misconstrued the application of decongestants and of expectorants in the products that it reviewed. The comment stated that decongestant ingredients have their activity in relieving nasal congestion via absorption and systemic distribution, and expectorant drugs have their activity in relieving bronchial secretion problems via reflex action stimulated in the stomach or via action in the pulmonary tree by absorption and systemic distribution. The effectiveness of these ingredients should not be part of the oral health care monograph, the comment concluded, but should be referred to the monograph for OTC cough-cold drug products.

The Oral Cavity Panel deferred most of the decongestant active ingredients to the Cough-Cold Panel because most of these ingredients are administered orally or topically (47 FR 22909). However, the Oral Cavity Panel found that some decongestant ingredients were combined with oral health care ingredients in the form of lozenges and felt that these decongestant ingredients could have topical activity on the mucous membranes of the mouth and throat. The Oral Cavity Panel did review two submissions on products containing phenylephrine hydrochloride and phenylpropanolamine hydrochloride as decongestants in lozenge form (Ref. 1). However, the two ingredients were present in lozenges that were labeled for the relief of nasal congestion, not congestion of the mouth or throat. Therefore, the agency agrees with the comment that the Oral Cavity Panel misconstrued the application of decongestant ingredients in these oral health care drug products and the data on decongestants should be referred to the nasal decongestant segment of the rulemaking for OTC cough-cold drug products. These decongestant ingredients will be discussed within the

context of the rulemaking for OTC nasal decongestant drug products in a future issue of the **Federal Register.**

Both the Cough-Cold Panel and the Oral Cavity Panel reviewed data on the safety and effectiveness of ingredients used as expectorants in OTC drug products. The Cough-Cold Panel reviewed 20 expectorants, classifying 6 in Category II and 14 in Category III. The Oral Cavity Panel reviewed only four expectorants, classifying one in Category II and three in Category III. The Cough-Cold Panel reviewed three of the four ingredients that were reviewed later by the Oral Cavity Panel. Both panels classified these three ingredients in the same categories. Because most of the expectorants had been reviewed earlier and more extensively by the Cough-Cold Panel, the agency agrees with the comment that the data on the effectiveness of expectorant active ingredients should be incorporated into the expectorant segment of the rulemaking for OTC cough-cold drug products. These ingredients will be discussed in the final monograph for OTC expectorant drug products, to be published in a future issue of the **Federal Register.**

Therefore, for the above reasons, and because no data were submitted in support of the effectiveness of any decongestant or expectorant ingredient for oral health care use, the agency is not including decongestants and expectorants in this tentative final monograph.

Reference

(1) OTC Volumes 130032 and 130058.

E. General Comments on Demulcent Drug Products

29. Citing the Panel's discussion of demulcents (47 FR 22915) as "* * * mucilaginous substances composed of gums, mucilages, starches, high molecular weight polymers of polyhydric alcohols, polysaccharides, certain saccharides * * *," one comment stated that sugars and sorbitol were overlooked by the Panel. The comment stated that two specific submissions to the Panel presented human clinical evidence supporting the demulcent action of sugar (Ref. 1) and sorbitol (Ref. 2), but that the Panel did not act on or respond to either of these submissions. The comment also referred to a study in which patients suffering with sore throat obtained pain relief with a plain, unflavored hard candy lozenge, a flavored hard candy lozenge, and a 2.4-mg hexylresorcinol lozenge (Ref. 3). The comment stated that in this study the demulcent effect of a sugar base lozenge was apparent both immediately after the dissolution of the lozenge and 5 minutes later.

The comment urged FDA to include sugars (such as sucrose, glucose, fructose, and dextrins) and sorbitol as approved demulcents in the oral health care rulemaking. In addition, the comment requested that, because sugars and sorbitol are usually the major components by weight in oral health care lozenges and syrups and because they are produced for and recognized as food substances, they should be allowed to be controlled for quality in accordance with the Current Good Manufacturing Practice (CGMP) regulations for foods, rather than for drugs. The comment also suggested an alternative approach that would allow demulcent claims for sugars and sorbitol when these ingredients form the major solid content of an oral health care drug product, but would not require their listing as active ingredients.

The agency has reviewed the studies (Refs. 1, 2, and 3) cited by the comment in support of its recommendation to include sugars and sorbitol as Category I demulcents in this rulemaking. The agency concludes that these studies provide insufficient data to support the effectiveness of sugars or sorbitol as Category I demulcents in lozenges or syrups when used in OTC oral health care drug products.

In the studies claimed by the comment to contain clinical evidence supporting the demulcent activity of sugars and sorbitol, the antitussive effectiveness of sugars and sorbitol was tested by the citric acid aerosol challenge-cough induction technique (Refs. 1 and 2). The agency concludes that these induction studies do not clearly demonstrate the demulcent effectiveness of sugars or sorbitol because the subjects studied did not have a sore mouth and sore throat. The Panel recommended the following indication for oral health care demulcents: "Aids in the temporary relief of minor discomfort and protects irritated areas in sore mouth and sore throat." Therefore, studies conducted to demonstrate the demulcent effect of ingredients must be conducted in the correct target population, i.e., subjects with a sore mouth or sore throat. The reduction of citric acid aerosol induced-cough does not demonstrate that an ingredient relieves sore mouth and sore throat symptoms by a demulcent action.

The multiclinic study mentioned by the comment, involving 225 volunteers in 3 separate medication groups, was designed to evaluate the safety and effectiveness of hexylresorcinol in the treatment of pain due to simple sore throat (Ref. 3). This double-blind, placebo-controlled study compared the effectiveness of a candy-based, 2.4-mg hexylresorcinol lozenge with two candy-based placebo lozenges, one flavored and one unflavored. The degree of relief from sore throat pain was subjectively evaluated immediately and 5 minutes after dissolution of each test lozenge. The agency's review of the results showed that there was some immediate subjective relief of sore throat pain in all groups tested and that the degree of relief was virtually the same in all three groups. At 5 minutes, the relief of sore throat pain provided by the hexylresorcinol lozenge was significantly better than the relief provided by the candy-based control lozenges ($p<0.05$); nevertheless, the control lozenges provided some sore throat relief. This study does not demonstrate the effectiveness of sugar as a demulcent in lozenges because the ingredients used to formulate the candy-based lozenges are not identified or quantitated and because both unmedicated lozenges were candy-based. Therefore, the study was not adequately designed or controlled and does not demonstrate the effectiveness of sugar in the form of a lozenge as a demulcent (Ref. 3).

In its report, the Panel included dextrose, sugar, and sorbitol as inactive ingredients or pharmaceutical necessities (47 FR 22764). The agency notes that sugars and sorbitol are usually considered pharmaceutical necessities in the manufacture and formulation of oral health care drug products. Although the data reviewed by the agency are inadequate to demonstrate the effectiveness of sugars or sorbitol as oral health care demulcents, the agency agrees with the comment that sugars and sorbitol may have demulcent activity when used in lozenge or syrup form. Therefore, the agency is proposing in this tentative final monograph to classify sugars and sorbitol as Category III demulcents when present as the major component of oral health care formulations such as a syrup or lozenge.

With regard to the comment's suggestion that sugars and sorbitol in OTC oral health care drug products should be controlled for quality in accordance with the CGMP regulations for foods (21 CFR Part 110), the agency notes that when sugars and sorbitol are included in products intended for use as food, they are required to meet the requirements of the CGMP regulations for foods. However, when sugars and sorbitol are used in the formulation of drug products, they are "components" (21 CFR 210.3(b)(3)) of the finished drug

products and, as such, they must meet all appropriate CGMP requirements applicable to drug components (21 CFR Parts 210 and 217).

Therefore, the agency recognizes that sugars and sorbitol can be included as inactive pharmaceutical ingredients in oral health care drug products. However, as stated above, the agency is also proposing to classify sugars and sorbitol in Category III as demulcents if demulcent claims are attributed to their presence in oral health care formulations such as syrups and lozenges.

The agency notes, however, that terms such as "soothing" may be used to describe the action of a sugar-based syrup or lozenge. This term is not a demulcent claim but describes certain physical and chemical attributes of a drug product and is distinctly separate from labeling indications. Terms describing product characteristics (e.g., color, odor, flavor, and feel) appear in the labeling for the consumers' information. Because such claims are not directly related to the safe and effective use of OTC oral health care drug products, the agency considers these claims to be outside the scope of the monograph. Any term that is outside the scope of the monograph may appear in any portion of the labeling not required by the monograph, but such labeling may not detract from the required information. Therefore, an OTC oral health care drug product could be described in the following manner in that portion of the labeling not required by the monograph: "A * * * drug product formulated in a soothing sugar (or sorbitol) base."

References

(1) OTC Volume 130095.

(2) OTC Volume 130146.

(3) Sabesin, S. M., and T. H. Weaber, Jr., "Multi-clinic SUCRETS Sore Throat Lozenge Study," draft of unpublished study, OTC Volume 130030.

F. General Comments on Combination Drug Products

30. Several comments objected to the Panel's recommendation in § 356.20(a), which allows an active ingredient identified in §§ 356.10 through 356.17 to be combined with one or more active ingredients from the same section in full or subtherapeutic doses only when "there is a clear demonstration that there is an improvement of safety or enhanced effectiveness or both." The comments contended that limited combinations to those that show enhanced safety or effectiveness conflicts with FDA's OTC drug review regulations in 21 CFR 330.10(a)(4)(iv) and with FDA's guidelines for OTC combination drug products (Ref. 1), which require only that each ingredient contributes to the claimed effect of the combination product.

Two comments noted that the Topical Analgesic Panel classified the combination of benzocaine and phenol in Category I. (See the **Federal Register** of December 4, 1979; 44 FR 69865.) The comments maintained that this combination should be allowed for oral health care use because phenol has a slower onset of action than benzocaine, but a longer duration of action; and benzocaine has a rapid onset, but a shorter duration of action. The comments acknowledged that proof of effectiveness is necessary if one or both ingredients are present at subtherapeutic levels. However, further testing is unwarranted if both ingredients are present at therapeutic levels because the ingredients supplement each other and thus have a broader activity.

One comment added that useful and acceptable combinations, such as benzocaine and menthol for sore throat (both anesthetic/analgesic active ingredients, but with different mechanisms of action), would be jeopardized by the Panel's recommended restriction. The comment also stated that there should not be a restriction against combining menthol with phenol, benzyl alcohol, or salicyl alcohol because menthol contributes cooling and palatability to a formulation, thus increasing patient acceptance. According to the comment, separating the contributions of the two drugs in terms of hard proof of enhanced safety would be extremely difficult and is unnecessary for compliance with the FDA guidelines. The comment stated that it interprets the guidelines to include patient acceptance, flavor, and other product improvements as some of the advantages allowed for combination drugs by the FDA guidelines. The comments recommended that the agency not adopt the Panel's recommendation regarding enhanced safety or effectiveness (§ 356.20(a)), but instead follow § 330.10(a)(4)(iv) and FDA's combination guidelines (Ref. 1).

Unlike the agency's combination guidelines, the Panel's recommendations in § 356.20(a) for combinations of ingredients from the same therapeutic category do not differentiate between a combination of ingredients from the same therapeutic category with the same mechanism of action and a combination of ingredients from the same therapeutic category with different mechanisms of action. The combination policy in § 330.10(a)(4)(iv), supplemented by the guidelines for OTC drug combination products (Ref. 1), will be used by the agency as the criterion for evaluating all OTC combination drug products.

The agency's guidelines do not require that combinations of ingredients from the same therapeutic category with different mechanisms of action demonstrate improved safety and/or enhanced effectiveness. Paragraph 2 of the guidelines provides that Category I active ingredients from the same therapeutic category that have different mechanisms of action may be combined to treat the same symptoms or condition if the combination meets the OTC combination policy in all respects and the combination is, on a benefit-risk basis, equal to or better than each of the active ingredients used alone at its therapeutic dose. Such combinations may utilize each active ingredient in full therapeutic or subtherapeutic dosage, as appropriate.

For combinations of ingredients from the same therapeutic category with the same mechanism of action, paragraph 3 of the guidelines states that such combinations should not ordinarily be combined unless there is some advantage over the single ingredients in terms of enhanced effectiveness, safety, patient acceptance, or quality of formulation. They may be combined in selected circumstances to treat the same symptoms or conditions if the combination meets the OTC combination policy in all respects, the combination offers some advantage over the active ingredients used alone, and the combination is, on a benefit-risk basis, equal to or better than each of the active ingredients used alone at its therapeutic dose.

For the above reasons, and based upon the requirements in § 330.10 and in the combination guidelines (Ref. 1), the agency is not proposing the Panel's Category I recommendation for the combinations in § 356.20(a). Instead, the agency is classifying all combinations containing two or more ingredients from the following pharmacologic groups in Category III except for specific combinations where data have shown a Category I classification is appropriate: anesthetic/analgesics identified in § 356.10, astringents identified in § 356.12, debriding agent/oral wound cleansers identified in § 356.14 (see comment 33 below), and demulcents identified in § 356.18. Decongestants identified in recommended § 356.15 and expectorants identified in recommended § 356.17 are not being included in this tentative final monograph but are being transferred to the rulemaking for OTC

cough-cold drug products. (See comment 28 above.)

The agency agrees with the comments that benzocaine and phenol, and benzocaine and menthol are allowable combinations of oral health care anesthetic/analgesic ingredients that conform to the requirements in § 330.10 and to the agency's combination guidelines (Ref. 1). Benzocaine and phenol or menthol are ingredients from the same therapeutic category but with different mechanisms of action. In its report, the Topical Analgesic Panel stated that "caine"-type drugs (e.g., benzocaine) and alcohol-type topical anesthetics (e.g., phenol and menthol) act at different receptor sites and that a combination of two may result in an effect that is greater than that produced if each ingredient were used alone (44 FR 69786). The Panel concluded that in combinations such as benzocaine and phenol or benzocaine and menthol, a contribution is made by each ingredient and that the attributes added to the combinations by the ingredients enhance the product's effectiveness and convey a noticeable benefit to the consumer (44 FR 69786). Despite a minority Panel report that disputed this reasoning (44 FR 69787 to 69790), the agency accepted the conclusions of the Panel majority and in the tentative final monograph for OTC external analgesic drug products, published in the **Federal Register** of February 8, 1983 (48 FR 5852), classified the combination of benzocaine with phenol or menthol in Category I. Because topical anesthetics behave similarly at different sites of the body (44 FR 69788), the agency believes that the combination of benzocaine with phenol or menthol should likewise enhance an oral cavity drug product's effectiveness, and that such combinations are at least as effective as each of the active ingredients used alone at its therapeutic dose.

The agency is aware that the mucous membranes are more permeable than the skin, and drugs are therefore more rapidly absorbed. Blood levels after application of local anesthetics to the mucous membranes simulate levels that would result from intravenous injection (Refs. 2, 3, and 4). Thus, the possibility of systemic effects occurring is greater from drugs used topically in the oral cavity than from those used on the intact skin. However, the agency believes that data submitted to the Oral Cavity Panel (Refs. 5 and 5) support the safety of the combination of benzocaine with phenol or menthol for use in the oral cavity. A combination drug product containing 6.67 percent benzocaine and 0.45 percent phenol was found to be non-toxic and non-irritating (Ref. 5). Rats and mice tolerated large doses given orally and repeated applications on rabbit gingiva caused no gross or microscopic changes on the gingival surface or beneath it. Another combination drug product containing 6.25 mg benzocaine and 2.5 mg menthol per lozenge was demonstrated to be non-toxic to dogs after intragastric administration (Ref. 6). In human safety studies, the combination drug product produced no significant adverse effects in a total of 742 subjects (Ref. 6). Therefore, the agency believes that the combination of benzocaine with phenol or menthol meets the OTC drug combination policy in all respects and is, on a benefit-risk basis, equal to or better than each of the active ingredients used alone.

Because menthol, phenol, benzyl alcohol, and salicyl alcohol are ingredients from the same therapeutic category with the same mechanism of action, these ingredients should nor normally be combined unless there is some advantage over the single ingredients in terms of enhanced effectiveness, safety, patient acceptance, or quality of formulation. The agency believes that because of its cooling effect, the use of menthol in combination with phenol, benzyl alcohol, or salicyl alcohol may enhance the consumer's acceptance of a drug product, but no data were submitted to the Panel or the agency demonstrating any advantage over the single ingredients for the combination of menthol with phenol, benzyl alcohol, or salicyl alcohol. The agency is, therefore, proposing a Category III classification for such combinations in this tentative final monograph. However, menthol, when used as an inactive ingredient, is generally recognized as safe as a flavorant in foods. (See 21 CFR 172.515 and 182.20.) Section 172.515 specifies that such flavoring substances be "used in the minimum quantity required to produce their intended effect and otherwise in accordance with all the principles of good manufacturing practice." These regulations do not specify an upper concentration for menthol used as a flavoring agent, and the agency is not proposing such a limit for OTC drug products at this time. However, the agency invites information and comments on (1) the minimum concentration of menthol needed to achieve a flavoring effect and (2) the minimum concentration needed to achieve a therapeutic effect. The agency will consider such information in determining how to distinguish between menthol as an active ingredient and whether to establish minimum levels. In any case, if menthol is present at a therapeutic level in a product, the agency would consider it to be an active ingredient in that product.

In summary, the agency is proposing the following Category III combinations in this tentative final monograph: menthol and phenol, benzyl alcohol, or salicyl alcohol. The following Category I combinations are being proposed in § 356.20:

(d) Benzocaine identified in § 356.10(b) may be combined with menthol identified in § 356.10(e).

(e) Benzocaine identified in § 356.10(b) may be combined with phenol identified in § 356.10(f).

References

(1) Food and Drug Administration, "General Guidelines for OTC Drug Combination Products," September 1978, Docket No. 78D–0322, Dockets Management Branch.

(2) Adriani, J., and H. Dalili, "Penetration of Local Anesthetics Through Epithelial Barriers," *Anesthesia and Analgesia*, 50:834–840, 1971.

(3) Adriani, J., "Some Aspects of Pharmacology of Local Anesthetics of Clinical Importance," *Marquette Medical Review*, 30:46–52, 1964.

(4) Adriani, J., and D. Campbell, "Fatalities Following Topical Application of Local Anesthetics to Mucous Membranes," *Journal of the American Medical Association*, 162:1527–1530, 1956.

(5) OTC Volume 130082.

(6) OTC Volume 130020.

31. One comment agreed with the Panel's recommendations in § 356.20 (d), (g), and (j) that combinations of nasal decongestants with anesthetics/analgesics and with antimicrobials are rational. It did not agree with the Panel's Category II classification of the combination of expectorants with anethetics/analgesics and furthermore believed that the following combinations which were not reviewed by the Panel should be Category I:

(1) Decongestants with demulcents;

(2) Expectorants with demulcents;

(3) Antihistamines with each of the pharmacological groups reviewed by the Panel; and

(4) Antitussives with each of the pharmacological groups reviewed by the Panel.

The Oral Cavity Panel considered only those combination drug products for which data were submitted pursuant to the notice published in the **Federal Register** on July 20, 1973 (39 FR 19444). The Panel recognized that other combination drug products may exist in the marketplace, but it lacked sufficient data concerning them to make a reasonable judgment of their safety and

effectiveness (47 FR 22791). Thus the Panel did not specifically address combination drug products containing a decongestant and a demulcent, an expectorant and a demulcent, or an antihistamine or an antitussive and any of the pharmacological groups reviewed by the Panel.

The agency recognizes that cold symptoms (e.g., nasal congestion, cough, and runny nose) and sore throat frequently occur concurrently and, for that reason, combinations of cough/cold active ingredients with oral health care active ingredients such as anesthetics/analgesics, antimicrobials, and demulcents may be rational. However, because such combination drug products are primarily cough-cold products, they are not being addressed in this document but will be discussed further in the tentative monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic combination drug products. The agency believes that labeling specific to cough-cold/oral health care combination drug products need only appear in one monograph, which should be the one most pertinent to the intended target population of the combination product. Therefore, the agency has determined that the labeling for cough-cold/oral health care combination products should be included in the combinations segment of the cough-cold tentative final monograph. Accordingly, the Panel's specific recommendations in § 356.20 (d), (g), and (j) of its monograph are not being addressed in this tentative final monograph. Further, the agency has stated in § 356.78(b)(1) that for oral health care/cough-cold combinations, the indications stated in the cough-cold monograph should be used.

32. Two comments requested that the Panel's recommended combinations of active ingredients identified in § 356.20 be expanded to include the following combinations in appropriate dosage forms: (1) Any anesthetic/analgesic active ingredient identified in § 356.10 may be combined with any internal analgesic active ingredient identified in § 343.10 and (2) any anesthetic/analgesic active ingredient identified in § 356.10 may be combined with any demulcent active ingredient identified in § 356.16 and with any internal analgesic active ingredient identified in § 343.10.

The comments stated that these are rational combinations because there are several different mechanisms of action that provide relief of sore throat pain. The comments explained that topical anesthetic/analgesic ingredients and demulcent ingredients would provide prompt pain relief, and internal analgesic ingredients would prolong the relief of pain for several hours.

The agency believes that the combinations listed above may be rational. However, the agency is not aware of any currently marketed OTC drug product that contain these combinations, and the comments provided no data to demonstrate the safety and effectiveness of any such combination. In this tentative final monograph, the agency is therefore proposing to classify the following combinations in Category III: (1) any anesthetic/analgesic combined with any internal analgesic and (2) any anesthetic/analgesic combined with any demulcent and any internal analgesic. The agency invites public comment on these combinations.

33. One comment noted that under § 356.20(a) of the Oral Cavity Panel's recommended monograph two debriding agents could be considered a Category I combination. The comment further noted, however, that the combination of two oral wound cleansers (which are the same ingredients and are used for the same purposes as debriding agents) is a Category II combination in the advance notice of proposed rulemaking for OTC oral mucosal injury drug products (44 FR 63276).

The comment supported a Category I classification for the combination of two active ingredients from the same therapeutic drug category when each active ingredient makes a contribution to the claimed effect, the safety or effectiveness of any active ingredient is not decreased, and the combination has some advantage over the single active ingredient. The comment requested that the monograph for oral mucosal injury drug products be corrected to allow the combination of two oral wound cleansers.

The agency is not proposing all of the Panel's recommended combinations in § 356.20(a) as Category I combinations. (See comment 30 above.) Rather, based upon the agency's general guidelines for OTC drug combination products (Ref. 1) and as stated in § 330.10, the agency is proposing Category III classification for combinations containing two or more ingredients from the same pharmacotherapeutic group with the same mechanism of action unless data show that the combination offers some advantage over the active ingredients used alone, and that the combination is, on a benefit-risk basis, equal to or better than each of the active ingredients used alone at its therapeutic dose. Also, as noted in comment 19 above, the agency is combining that part of the rulemaking for OTC oral mucosal injury drug products that includes oral wound cleansers with the rulemaking for OTC oral health care drug products and is creating a new class of drugs called debriding agent/oral wound cleanser drug products. The agency concludes that there is no basis for classifying the combination of two or more debriding agent/oral wound cleanser ingredients in Category I and is proposing to classify that combination in Category III in this tentative final monograph to allow for further comments and the submission of data to support such a combination.

Therefore, if the data are submitted that justify the combination of two or more debriding agent/oral wound cleansers, that combination will be reclassified from Category III to Category I in the final monograph.

Reference

(1) Food and Drug Administration, "General Guidelines for OTC Drug Combination Products," September 1978, Docket No. 78D–0322, Dockets Management Branch.

34. One comment recommended that FDA reinstate the acceptability of a combination of debriding agents and demulcent agents, which was recognized in the Panel's drafts on combinations. As an example, the comment noted that in one product submitted to the Panel a demulcent recognized by the Panel (glycerin) is also the vehicle providing a stable dosage form of a debriding agent (carbamide peroxide).

The Panel's published report, rather than its working drafts, represents its final conclusions and recommendations to FDA. The combination of a debriding agent with a demulcent was not specifically discussed in the Panel's report, nor did the Panel classify as Category I any combination containing a debriding agent. In fact, the Panel classified several combinations containing debriding agents in Category II. It concluded that a debriding agent, because of its mechanical cleansing action, would wash away or dilute the other active ingredients in the combination and thus prevent them from acting as intended or from exerting their therapeutic effects (47 FR 22792.) The agency agrees with the Panel.

Regarding the comment's specific example, carbamide peroxide in anhydrous glycerin, the agency concludes that anhydrous glycerin is a pharmaceutical necessity used for the sole purpose of stabilizing the carbamide peroxide and as such is not considered to be an active ingredient in this product. Such products would contain only one active ingredient

(carbamide peroxide) and would not be considered a combination of a debriding agent and a demulcent.

For the reasons above, the agency is proposing that combinations of debriding agent/oral wound cleansers and demulcents be classified Category II.

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 Oral Cavity Panel and oral wound cleanser ingredients submitted to the Dental Panel as well as other data and information available at this time, and has made the following changes in the categorization of oral health care (anesthetic/analgesic, astringent, debriding agent/oral wound cleanser, decongestant, demulcent, and expectorant) active ingredients recommended by the Panels. The agency is combining debriding agents reviewed by the Oral Cavity Panel and oral wound cleansers reviewed by the Dental Panel into one therapeutic group, debriding agent/oral wound cleansers. The agency is proposing to reclassify sodium perborate monohydrate, 1.2 g, used as a debriding agent/oral wound cleanser, from Category II to Category I. The agency is proposing to reclassify aspirin in a chewing gum base, used as a topical anesthetic/analgesic, from Category I to Category III for effectiveness. Aspirin in a chewing gum base remains in Category I for safety when used as a topical anesthetic/analgesic. In addition, the agency is not including decongestant or expectorant ingredients in this rulemaking but is transfering them to the rulemaking for OTC cough-cold drug products. As a convenience to the reader, the following list is included as a summary of the categorization of oral health care (anesthetic/analgesic, astringent, debriding agent/oral wound cleanser, decongestant, demulcent, and expectorant) active ingredients proposed by the Panel and the agency.

Oral health care active ingredients	Panel	FDA
Oral health care anesthetic/analgesics:		
Antipyrine	II	II
Aspirin	I	III
Benzocaine	I	I
Benzyl alcohol	I	I
Camphor	II	II
Cresol	II	II
Dibucaine	II	II
Dibucaine hydrochloride	II	II
Dyclonine hydrochloride	I	I
Eucalyptol (eucalyptus oil)	III	III
Hexylresorcinol	I	I
Lidocaine	II	II
Lidocaine hydrochloride	II	II
Menthol	I	I
Methyl salicylate	III	III
Phenol preparations (phenol and/or phenolate sodium)	I	I
Pyrilamine maleate	II	II
Salicyl alcohol	I	I
Tetracaine	II	II
Tetracaine hydrochloride	II	II
Thymol	III	III
Oral health care astringents:		
Alum	I	I
Myrrh Tincture	II	II
Zinc chloride	I	I
Oral health care debriding agent/oral wound cleanser:		
Carbamide peroxide in anhydrous glycerin	I	I
Hydrogen peroxide	I	I
Sodium bicarbonate	I	I
Sodium perborate monohydrate	II	I
Oral health care decongestants:		
Phenylephrine hydrochloride	III	R[1]
Phenylpropanolamine hydrochloride	III	R[1]
Oral health care demulcents:		
Elm bark	I	I
Gelatin	I	I
Glycerin	I	I
Pectin	I	I
Sugars (sucrose, dextrose, fructose, and dextrins)	(2)	III
Sorbitol	(2)	III
Oral health care expectorants:		
Ammonium chloride	III	R[1]
Horehound	III	R[1]
Potassium iodide	II	R[1]
Tolu balsam	III	R[1]

[1] R—Referred to the rulemaking for OTC cough-cold drug products.
[2] Not reviewed.

2. *Testing of Category II and Category III conditions.* The Oral Cavity Panel recommended testing guidelines for OTC oral health care drug products (47 FR 22781 to 22784) and testing guidelines for OTC oral health care anesthetic/analgesic drug products (47 FR 22830 to 22831). The Dental Panel recommended testing guidelines for OTC oral mucosal injury drug products (44 FR 63287 to 63289). 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 submissions of data and information to demonstrate the safety or effectiveness of any OTC oral health care anesthetic/analgesic, astringent, debriding agent/oral wound cleanser, or demulcent active 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 submissions 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. Because of the overlap and similarities in the definitions, therapeutic use, mechanisms of action, and site of action of oral wound cleansers and debriding agents, the agency has decided to incorporate portions of the rulemaking for OTC oral mucosal injury drug products into this tentative final monograph for OTC oral health care drug products. The agency is combining the definition of oral wound cleansers proposed in § 353.3 of the tentative final monograph for OTC oral mucosal injury drug products and the definition of a debriding agent recommended by the Oral Cavity Panel in § 356.3(e) and is proposing the combined definition for debriding agent/oral wound cleansers in § 356.3 of this tentative final monograph. The agency is also reproposing, with minor modification, the indications, warnings, and directions from § 353.50 and the professional labeling from § 353.80 of the tentative final monograph for OTC oral mucosal injury drug products in § 356.70 and § 356.80 respectively of this tentative final monograph. (See comments 19 and 25 above.)

The agency is deferring consideration of recommended § 353.20(b), regarding the combination of an oral wound cleanser and an antiseptic, to the

antimicrobial segment of the rulemaking for OTC oral health care drug products.

The agency addressed oral wound healing agents in a final rule published in the **Federal Register** of July 18, 1986 (51 FR 26112). (See comment 19 above.)

2. The agency is transferring decongestant and expectorant ingredients to the rulemaking for OTC cough-cold drug products. Therefore, the agency is not including §§ 356.3(f) and (h), 356.15, 356.17, 356.20(d), (g), and (j), 356.55, and 356.57 of the advance notice of proposed rulemaking in this tentative final monograph. The agency will discuss decongestants within the context of the rulemaking for OTC nasal decongestant drug products that will be published in a future issue of the **Federal Register.** The agency will discuss expectorants in the final monograph for OTC expectorant drug products that will be published in a future issue of the **Federal Register.** (See comments 28 and 31 above.)

3. In this tentative final monograph, the agency is deleting the words "health care" from the statements of identity in §§ 356.55(a), 356.65(a), 356.70(a), and 356.75(a). The agency believes that the word "oral" is the key word in the statements of identity for oral health care drug products and that the words "health care" are excessive and unnecessary.

4. The agency is classifying aspirin (in a chewing gum base) in Category III for effectiveness and in Category I for safety. Therefore, the agency is not including the Panel's recommended §§ 356.10(a) and 356.50(a)(1), (c)(2), and (d)(1) in this tentative final monograph. (See comment 15 above.)

5. The agency agrees with the Oral Cavity Panel's recommendation that systemic relief of minor sore throat pain should be addressed in the rulemaking for OTC internal analgesic, antipyretic, and antirheumatic drug products and is transferring all comments and associated submissions regarding internal analgesic ingredients for the relief of minor sore throat pain to that rulemaking (Docket No. 77N–0094) for further evaluation. (See comment 14 above.)

6. The agency is revising the descriptions of carbamide peroxide in the Panel's recommended §§ 356.14(a) and 356.54(d)(1) and is proposing, in this tentative final monograph, that § 356.16(a) read as follows, "Carbamide peroxide in anhydrous glycerin." Reference to a solution of carbamide peroxide in water is not being included in the directions proposed in § 356.70(d)(1). (See comment 24 above.)

7. Phenol identified in recommended § 356.10(g) and phenolate sodium identified in recommended § 356.10(h) are being replaced by "Phenol preparations (phenol and/or phenolate)" in proposed § 356.10(f) of this tentative final monograph. (See comment 9 above.)

8. The agency is reclassifying sodium perborate monohydrate from Category II to Category I based upon the agency's evaluation of sodium perborate monohydrate as an oral wound cleanser and is including sodium perborate monohydrate, 1.2 g to be dissolved in 30 mL water in § 356.16(d) as a debriding agent/oral wound cleanser. The agency is including directions for use of sodium perborate monohydrate as a debriding agent/oral wound cleanser in § 356.70(d)(4) of this tentative final monograph. (See comment 22 above.)

9. The agency is classifying concentrations of less than 2 mg menthol in a solid dosage form for use as an anesthetic/analgesic active ingredient in Category III. (See comment 12 above.)

10. The agency is classifying sugars and sorbital in solid and nonsolid dosage forms for use as a demulcent in Category III. (See comment 29 above.)

11. The agency is inviting the submission of data in support of a minimum dosage of 5 mg benzyl alcohol per solid dosage form. (See comment 13 above.)

12. The agency is not accepting the Panel's Category I recommendation for the combinations it included in § 356.20(a) and is instead proposing a Category III classification for those combinations that contain two or more ingredients from the same pharmacological group except in specific cases where data have shown a Category I classification is appropriate. As a result, the agency is classifying combinations containing two or more ingredients from the following pharmacological groups in Category III: anesthetic/analgesics in § 356.10, astringents in § 356.14, debriding agent/oral wound cleansers in § 356.16, and demulcents in § 356.18. (See comments 30 and 33 above.)

13. The agency is proposing to classify the following combinations in Category I: benzocaine and phenol or menthol. (See comment 30 above.)

14. In this tentative final monograph, the agency is classifying the following combinations in Category III: menthol and benzyl alcohol, phenol, or salicyl alcohol; an anesthetic/analgesic and an internal analgesic; and an anesthetic/analgesic, an internal analgesic, and a demulcent. (See comments 30 and 32 above.)

15. The agency is proposing a Category II classification for the combination of a debriding agent/oral wound cleanser and demulcent. (See comment 34 above.)

16. Because combinations of cough-cold active ingredients with oral health care active ingredients are primarily cough-cold products, they are not being discussed in this document but will be addressed in the tentative final monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic combination drug products to be published in a future issue of the **Federal Register.** Therefore, § 356.20 (d), (g), and (j) of the Panel's recommended monograph are not being proposed in this tentative final monograph. The agency is instead proposing § 356.20(g) which refers to § 341.40 for oral health care and cough-cold combinations and to § 356.78(b)(1) which states that for oral health care/cough-cold combinations, the indications stated in the cough-cold monograph should be used. (See comment 31 above.)

17. To encompass the variety of different solid dosage forms (lozenges, compressed tablets) and nonsolid dosage forms (mouthwashes, gels) that may be used as OTC oral health care drug products, the agency is using the terms "solid dosage forms" and "dosage forms other than solid," and is not using specific dosage form terms such as rinse, mouthwash, lozenge, etc., in §§ 356.55(d), 356.65(d), 356.70(d), and 356.75(d) of the tentative final monograph except where the identification of a specific dosage form is relevant to the use, safety, or effectiveness of the ingredient. (See comment 11 above.)

18. The warning recommended by the Panel in §§ 356.50(c)(3), 356.52(c)(2), 356.54(c)(2), and 356.56(c)(2) is not being included in this tentative final monograph. Instead, the agency is proposing the phrase "and then spit out" in appropriate places in the directions in §§ 356.55(d), 356.65(d), 356.70(d), and 356.75(d) of this tentative final monograph. (See comment 3 above.)

19. The agency is proposing that the lower age limit for use of all OTC oral health care drug products included in this tentative final monograph by 2 years, except for sodium perborate monohydrate and except for phenol preparations that are intended for ingestion or that could be inadvertently ingested. (See comment 22 above and Change No. 22 below.) In addition, in order to be consistent with labeling proposed for debriding agent/oral wound cleansers, the agency is deleting any reference to age limits from the warnings proposed for the OTC oral health care products included in this

tentative final monograph and is, instead, including age requirements in the directions for use in §§ 356.55(d), 356.65(d), 356.70(d), and 356.75(d). (See comment 26 above.)

20. The agency believes that children under 12 years of age should be supervised in the use of OTC oral health care nonsolid dosage forms. This restriction was recommended by the Dental Panel in the advance notice of proposed rulemaking for OTC oral mucosal injury drug products (44 FR 63278), and the agency agrees with that Panel. Therefore, in this tentative final monograph for oral health care drug products, the agency is proposing the phrase "Children under 12 years of age should be supervised in the use of the product" in all directions for use of dosage forms other than solid.

21. The agency believes the oral health care drug products in a dosage form other than solid should be gargled, swished around the mouth (affected area), or allowed to stay in place for at least 1 minute in order to exert their effect in the oral cavity, except for phenol which has been shown to exert its effect or the oral cavity in 15 seconds. (See Change No. 22 below.) Therefore, the agency is proposing such wording in the directions in §§ 356.55(d), 356.65(d), 356.70(d), and 356.75(d). The word "gargle" is not included in § 356.70(d) because debriding agent/oral wound cleansers are not indicated for the relief or sore throat symptoms. (See comment 26 above.)

22. The warnings recommended by the Panel in §§ 56.50(c)(1) (i) and (ii), 356.52(c)(1) (i) and (ii), and 356.56(c)(1) (i) and (ii) are not being included in this tentative final monograph. In order to limit the number of warnings and to simplify labeling so that only essential information is required, the agency is proposing to combine those warnings. Additionally, because OTC oral health care drug products other than debriding agent/oral wound cleansers may be used to relieve conditions associated with either sore throat or sore mouth, the agency believes that, in addition to the 2-day warning statement associated with sore throat symptoms, another statement would be useful to reflect the less serious nature of sore mouth symptoms. (For discussion of sore mouth symptoms, see comment 26 above.) Therefore, the agency is proposing the following revised warning in §§ 356.55(c)(1), 356.65(c), and 356.75(c) of this tentative final monograph: "If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea, or vomiting, consult a doctor promptly. If sore mouth symptoms do not improve in 7 days, see your dentist or doctor promptly." The agency is proposing in § 356.55(c)(2) a slightly different warning for anesthetic/analgesic drug products labeled only "for temporary relief of pain associated with canker sores." [The section numbers recommended by the Panel have been redesignated in this tentative final monograph.]

23. In this tentative final monograph the agency is including the following indication for OTC oral anesthetic/analgesic active ingredients in § 356.50(b): "For temporary relief of pain associated with canker sores." (See comment 6 above.)

24. Instead of the Panel's recommended directions for use of phenol and phenolate sodium in § 356.50(d) (7) and (8), the agency is revising those directions and including them in proposed § 356.55(d)(6) of this tentative final monograph. The agency believes that although phenol-containing oral health care drug products for local application (such as a spray or locally applied gel) may be used in children 2 years of age and older, phenol-containing oral health care products that are intended for ingestion (solid dosage forms) or that could be inadvertently ingested (mouthwashes) should not be used in children under 6 years of age except under the supervision of a dentist or doctor.

Although the amount of drug products used for local application in the oral cavity is small (usually less than 1 mL), the amount of product used as a mouthwash or oral rinse may be 10 to 25 mL. Children have been reported to be more sensitive to phenol toxicity than adults (Ref. 1), and children are more likely to swallow a liquid drug product (44 FR 63278). The Dental Panel stated that, for children under 6 years of age, there was no recommended dosage for phenol for use as a dental rinse except under the supervision of a dentist or doctor (47 FR 22759). In addition, the labeling of currently marketed OTC oral health care drug products containing phenol restricts use of the product to adults and children over 6 years of age (Ref. 2).

Therefore, the agency is proposing to restrict the use of phenol-containing lozenges (solid dosage form) and the use of nonsolid dosage forms (such as oral rinses or mouthwashes) to children 6 years of age and older. However, phenol-containing nonsolid dosage forms intended for local application (such as sprays or locally applied gels) may be used by children 2 years of age and older. Moreover, the agency is proposing to restrict the amount of phenol-containing oral rinse or mouthwash that children 6 to 12 years of age may use to 10 mL per application so that the maximum pediatric dosage of 300 mg per day is not exceeded. The agency does not believe that it is necessary to restrict the amount of liquid dosage form used by adults. (See comment 10 above.)

Furthermore, the agency believes that the anesthetic effectiveness of phenol depends not only upon the dosing frequency but also upon the contact time per dose. Therefore, the agency is proposing at least a 15-second contact time for each application of a phenol-containing dosage form other than solid (Refs. 2 and 3). (For additional discussion of rinse times, see comment 10 above.) The agency is proposing the following directions for OTC oral health care anesthetic/analgesic drug products containing phenol and/or phenolate sodium in § 356.55(d)(6) of this tentative final monograph:

(i) *For dosage forms other than solid, the product is an aqueous solution or suspension containing phenol or phenolate sodium equivalent to 0.5- to 1.5-percent phenol—(a) For direct application.* Adults and children 2 years of age and older: Apply to the affected area, allow to remain in place for at least 15 seconds and then spit out. Use every 2 hours 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.

(*b*) *For use as a mouthwash (oral rinse).* Adults and children 12 years of age and older: Gargle or swish around the mouth for at least 15 seconds and then spit out. Use every 2 hours or as directed by a dentist or doctor. Children 6 to under 12 years of age: Apply 10 milliliters to the affected area, gargle or swish around the mouth for at least 15 seconds and then spit out. Use every 2 hours 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.

(ii) *For solid dosage forms, the product (lozenge or tablet) contains phenol or phenolate sodium equivalent to 10 to 50 milligrams phenol.* Adults and children 12 years of age and older: Allow the product (lozenge or tablet) to dissolve slowly in the mouth. May be repeated every 2 hours or as directed by a dentist or doctor. Children 6 to under 12 years of age: Allow product lozenge or tablet to dissolve slowly in the mouth. May be repeated every 2 hours, not to exceed 300 milligrams phenol in 24 hours, or as directed by a dentist or doctor. Children under 6 years of age: Consult a dentist or doctor.

References

(1) Solis-Cohen, S., and T. S. Githens, "Pharmacotherapeutics," in "Materia Medica and Drug Action," D. Appleton and Co New York, p. 750, 1928.

(2) OTC Volume 13 ATFM.

(3) Bronsky, D. A., "To Evaluate the Efficacy of Both Chloraseptic Solution and Chloraseptic Lozenges When Used to Relieve the Gingival and Buccal Mucosal Discomfort Associated with Orthodontic Braces," draft of unpublished study, C00014, Docket No. 80N-0033, Dockets Management Branch.

25. Because debriding agent/oral wound cleansers have not historically been indicated for use in the relief of sore throat symptoms, and because the therapeutic benefits of using these ingredients for sore throat symptoms are not apparent, the agency is proposing that debriding agent/oral wound cleansers be limited to use only in relieving symptoms associated with sore mouth. (See comment 26 above.) The agency is proposing the following indications for debriding agent/oral would cleansers in § 356.70(b) of this tentative final monograph:

(1) "Aids in the removal of phlegm, mucus, or other secretions associated with occasional sore mouth."

(2) "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."

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

26. The agency is proposing that debriding agent/oral wound cleansers can be safely used for up to 7 days before seeking professional guidance because debriding agent/oral wound cleansers are indicated only for removal of foreign material associated with sore mouth, and sore mouth symptoms are unlikely to be indicative of serious health threats. In addition, the agency is proposing that the lower age limit for use of debriding agent/oral wound cleansers, except sodium perborate monohydrate (see comment 22 above), be 2 years of age, and that because the age limitations are included in the directions, they need not be included in a warning statement.

Because debriding agent/oral wound cleansers are not indicated for sore throat symptoms, the agency is not including in this tentative final monograph the warning statement recommended by the Panel in § 356.54(c)(1)(i). Instead, the agency is combining the warning recommended in § 353.50(c) of the tentative final monograph for OTC oral mucosal injury drug products with the Panel's recommended warning in § 356.54(c)(1)(ii), to read as follows: "Do not use this product for more than 7 days unless directed by a dentist or doctor. If sore mouth symptoms do not improve in 7 days; if irritation, pain, or redness persists or worsen; or if swelling, rash, or fever develops, see your dentist or doctor promptly" and is including this warning in § 356.70(c) of this tentative final monograph. (See comment 26 above.)

27. The agency is not accepting the directions for use for carbamide peroxide and hydrogen peroxide recommended by the Panel in § 356.54(d) (1) and (2). Instead, the directions recommended by the agency for carbamide peroxide and hydrogen peroxide as oral wound cleansers in § 353.50(d) (1) and (2) of the tentative final monograph for OTC oral mucosal injury drug products, with minor modifications, are being proposed in § 356.70(d) (1) and (2) of this tentative final monograph. (See comment 27 above.)

28. The agency is proposing the following additional indications for anesthetic/analgesic ingredients identified in § 356.10 in § 356.80 *Professional labeling* in this tentative final monograph: "For the temporary relief of pain associated with any one or more of the following conditions; tonsilitis, pharyngitis, throat infections, and stomatitis." (See comment 5 above.)

29. As a result of incorporating portions of the rulemaking for OTC oral mucosal injury drug products into this tentative final monograph, the agency is adding a section, § 356.70(b)(4), to the debriding agent/oral wound cleanser section of this tentative final monograph entitled "Other allowable statements" to include the following statements that were proposed in the tentative final monograph for OTC oral mucosal injury drug products: "Assists in the removal of foreign material from minor oral wounds" and "Physically removes debris from minor oral wounds."

30. Combining the oral health care rulemaking (proposed Part 356) and the oral mucosal injury rulemaking (proposed Part 353) into the present tentative final monograph under proposed 21 CFR Part 356 (entitled "Oral Health Care Drug Products for OTC Human Use") and deferring decongestant and expectorant active ingredients and cough-cold/oral health care combination drug products to other rulemakings has resulted in the redesignation of many section and paragraph numbers. The agency is also designating proposed Subpart D of the monograph as Subpart C and is placing the labeling sections under Subpart C.

31. 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 is proposing to remove the existing warning and caution statements required by § 369.20 for "sodium perborate (sodium perborate monohydrate) mouthwash and gargle and toothpaste" and for "throat preparations for temporary relief of minor sore throat: lozenges, troches, washes, gargles, etc." and the suggested warning for over-the-counter drugs for minor sore throats in § 201.315 because the conditions in those sections will be superseded by the requirements of the final monographs on OTC oral health care drug products (Part 356, Subpart C) and OTC relief of oral discomfort drug products (Part 354, Subpart C).

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 health care anesthetic/analgesic, astringent, debriding agent/oral wound cleanser, and demulcent 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, Public Law 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 health care anesthetic/analgesic astringent, debriding agent/oral wound cleanser, and demulcent 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 invited public comment in the advance notice of proposed rulemaking regarding any impact that this rulemaking would have on OTC oral health care anesthetic/analgesic, astringent, debriding agent, and demulcent drug products. It also invited public comment in the tentative final monograph for OTC oral mucosal injury drug products regarding any impact that this rulemaking would have an OTC oral mucosal injury drug products. No comments on economic impacts were received in response to either request. Any comments on the agency's initial determination of the economic consequences of this proposed rulemaking should be submitted by May 26, 1988. 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 carefully considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday. This action was considered under FDA's final rule implementing the National Environmental Policy Act (21 CFR Part 25).

Interested persons may, on or before May 26, 1988, submit to the Dockets Management Branch (HFA-305), Food and Drug Administration, Room 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 May 26, 1988. 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 announced in the **Federal Register**.

Interested persons, on or before January 27, 1989, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before March 27, 1989. 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 March 27, 1989. 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.

List of Subjects

21 CFR Part 201

Drugs, Labeling.

21 CFR Part 356

Labeling, Over-the-counter drugs, Oral health care drug products.

21 CFR Part 369

OTC drugs, Warning and caution statements.

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

PART 201—LABELING

1. The authority citation for 21 CFR Part 201 is revised to read as follows:

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

§ 201.315 [Removed]

2. Subpart G is amended by removing § 201.315 *Over-the-counter drugs for minor sore throats; suggested warning.*

3. By adding new Part 356, to read as follows:

PART 356—ORAL HEALTH CARE DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Sec.
356.1 Scope.
356.3 Definitions.

Subpart B—Active Ingredients

356.10 Anesthetic/analgesics.
356.14 Astringents.
356.16 Debriding agent/oral wound cleansers.
356.18 Demulcents.
356.20 Permitted combinations of active ingredients.

Subpart C—Labeling

356.50 Labeling of oral health care drug products.
356.55 Labeling of anesthetic/analgesic drug products.
356.65 Labeling of astringent drug products.
356.70 Labeling of debriding agent/oral wound cleanser drug products.
356.75 Labeling of demulcent drug products.
356.78 Labeling of combination drug products.
356.80 Professional 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); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

Subpart A—General Provisions

§ 356.1 Scope.

(a) An over-the-counter oral health care drug product in a form suitable for topical administration is generally recognized as safe and effective and is not misbranded if it meets each condition in this part and each general condition 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.

§ 356.3 Definitions.

As used in this part:

(a) *Oral health care drug.* A drug product applied topically for the proper care of the oral cavity, including the temporary relief of symptoms of the mouth and throat, for example, occasional minor sore throat or mouth soreness.

(b) *Anesthetic/analgesic.* A substance applied topically to an epithelial surface (e.g., skin or mucous membrane) that relieves pain without necessarily

abolishing other sensations (analgesic) or a substance applied topically that completely blocks pain receptors resulting in a sensation of numbness and abolition of response to painful stimuli (anesthetic).

(c) *Anhydrous glycerin.* An ingredient that may be prepared by heating glycerin U.S.P. at 150 °C for 2 hours to drive off the moisture content.

(d) *Astringent.* An agent that causes contraction of the tissues or arrest of secretions by coagulation of proteins on a cell surface.

(e) *Debriding agent/oral wound cleanser.* A nonirritating agent which causes or assists in the removal (physically or chemically) of foreign material or devitalized or contaminated tissue from or adjacent to a minor oral wound or a traumatic or infected lesion to expose surrounding healthy tissue and does not delay wound healing.

(f) *Demulcent.* A bland, inert agent that soothes and relieves irritation of inflamed or abraded surfaces such as mucous membranes.

(g) *Mouthwash (oral rinse).* A solution used for rinsing the mouth, not necessarily for medicinal purposes.

(h) *Oral cavity (mouth).* The cavity of the mouth and associated structures, including the cheeks, palate, oral mucosa, glands where ducts open into it, the teeth, and the tongue.

Subpart B—Active Ingredients

§ 356.10 Anesthetic/analgesics.

The active ingredient of the product consists of any of the following when used within the dosage limits and in the dosage form established for each ingredient in § 356.55(d).

(a) Benzocaine.

(b) Benzyl alcohol.

(c) Dyclonine hydrochloride.

(d) Hexylresorcinol.

(e) Menthol.

(f) Phenol preparations (phenol and/or phenolate sodium).

(g) Salicyl alcohol.

§ 356.14 Astringents.

The active ingredient of the product consists of any of the following when used within the dosage limits and in the dosage form established for each ingredient in § 356.65(d).

(a) Alum.

(b) Zinc chloride.

§ 356.16 Debriding agent/oral wound cleansers.

The active ingredient of the product consists of any of the following when used within the dosage limits and in the dosage form established for each ingredient in § 356.70(d).

(a) Carbamide peroxide in anhydrous glycerin.

(b) Hydrogen peroxide.

(c) Sodium bicarbonate.

(d) Sodium perborate monohydrate.

§ 356.18 Demulcents.

The active ingredient of the product consists of any of the following when used within the dosage limits and in the dosage form established for each ingredient in § 356.75(d):

(a) Elm bark.

(b) Gelatin.

(c) Glycerin.

(d) Pectin.

§ 356.20 Permitted combinations of active ingredients.

(a) Any anesthetic/analgesic active ingredient identified in § 356.10 may be combined with any astringent active ingredient identified in § 356.14.

(b) Any anesthetic/analgesic active ingredient identified in § 356.10 may be combined with any demulcent active ingredient identified in § 356.18.

(c) Benzocaine identified in § 356.10(a) may be combined with menthol identified in § 356.10(e).

(d) Benzocaine identified in § 356.10(a) may be combined with phenol preparations identified in § 356.10(f).

(e) Oral health care and cough-cold combinations. See § 341.40.

Subpart C—Labeling

§ 356.50 Labeling of oral health care drug products.

(a) The word physician may be substituted for the word doctor in any of the labeling statements in this part.

(b) Where applicable, indications in this part applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this part, may also be used, as provided in § 330.1(c)(2), subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(c) Warnings and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable.

§ 356.55 Labeling of anesthetic/analgesic drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "oral anesthetic," an "oral anesthetic/analgesic," or an "oral pain reliever."

(b) *Indications.* The labeling of the product states, under the heading "Indications," either or both of the following:

(1) "For temporary relief of occasional minor irritation, pain, sore mouth, and sore throat."

(2) "For temporary relief of pain associated with canker sores."

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

(1) *For all products containing any ingredient identified in § 356.10.* "If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea, or vomiting, consult a doctor promptly. If sore mouth symptoms do not improve in 7 days, see your dentist or doctor promptly."

(2) *For all products containing any ingredient identified in § 356.10 labeled with only the indication in § 356.55(b)(2).* "Do not use this product for more than 7 days unless directed by a dentist or doctor. If sore mouth symptoms do not improve in 7 days; if irritation, pain, or redness persists or worsens; or if swelling, rash 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 benzocaine identified in § 356.10(a)*—(i) *For dosage forms other than solid, the product is a 5- to 20-percent solution or suspension.* Adults and children 2 years of age and older: Apply to the affected area. Gargle, swish around in the mouth, or allow to remain in place at least 1 minute and then spit out. Use up to 4 times daily 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.

(ii) *For solid dosage forms, the product contains 2 to 15 milligrams benzocaine.* Adults and children 2 years of age and older: Allow product to dissolve slowly in the mouth. May be repeated every 2 hours as needed or as directed by a dentist or doctor. Children under 2 years of age: Consult a dentist or doctor.

(2) *For products containing benzyl alcohol identified in § 356.10(b)*—(i) *For*

dosage forms other than solid, the product is a 0.05- to 10-percent solution or suspension. Adults and children 2 years of age and older: Apply to the affected area. Gargle, swish around, or allow to remain in place at least 1 minute and then spit out. Use up to 4 times daily 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.

(ii) *For solid dosage forms, the product contains 100 to 500 milligrams benzyl alcohol.* Adults and children 2 years of age and older: Allow product to dissolve slowly in the mouth. May be repeated every 2 hours as needed or as directed by a dentist or doctor. Children under 2 years of age: Consult a dentist or doctor.

(3) *For products containing dyclonine hydrochloride identified in § 356.10(c)*—(i) *For dosage forms other than solid, the product is a 0.05- to 0.10-percent solution or suspension.* Adults and children 2 years of age and older: Apply to the affected area. Gargle, swish around, or allow to remain in place at least 1 minute and then spit out. Use up to 4 times daily 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 solid dosage forms, the product contains 1 to 3 milligrams dyclonine hydrochloride.* Adults and children 2 years of age and older: Allow product to dissolve slowly in the mouth. May be repeated every 2 hours as needed or as directed by a dentist or doctor. Children under 2 years of age: Consult a dentist or doctor.

(4) *For products containing hexylresorcinol identified in § 356.10(d)*—(i) *For dosage forms other than solid, the product is a 0.05- to 0.1-percent solution or suspension.* Adults and children 2 years of age and older: Apply to the affected area. Gargle, swish around, or allow to remain in place at least 1 minute and then spit out. Use up to 4 times daily 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.

(ii) *For solid dosage forms, the product contains 2 to 4 milligrams hexylresorcinol.* Adults and children 2 years of age and older: Allow product to dissolve slowly in the mouth. May be repeated every 2 hours as needed or as directed by a dentist or doctor. Children under 2 years of age: Consult a dentist or doctor.

(5) *For products containing menthol identified in § 356.10(e)*—(i) *For dosage forms other than solid, the product is a 0.04- to 2-percent solution or suspension.* Adults and children 2 years of age and older: Apply to the affected area. Gargle, swish around, or allow to remain in place at least 1 minute and then spit out. Use up to 4 times daily 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 solid dosage forms, the product contains 2 to 20 milligrams menthol.* Adults and children 2 years of age and older: Allow product to dissolve slowly in the mouth. May be repeated every 2 hours as needed or as directed by a dentist or doctor. Children under 2 years of age: Consult a dentist or doctor.

(6) *For products containing phenol preparations identified in § 356.10(f)*—(i) *For dosage forms other than solid, the product is an aqueous solution or suspension containing phenol or phenolate sodium equivalent to 0.5- to 1.5-percent phenol*—(A) *For direct application.* Adults and children 2 years of age and older: Apply to the affected area. Gargle, swish around, or allow to remain in place at least 15 seconds and then spit out. Use every 2 hours 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.

(B) *For use as a mouthwash (oral rinse).* Adults and children 12 years of age and older: Apply to the affected area. Gargle, swish around the mouth for at least 15 seconds and then spit out. Use every 2 hours or as directed by a dentist or doctor. Children 6 to under 12 years of age: Apply 10 milliliters to the affected area, gargle, or swish around the mouth for at least 15 seconds and then spit out. Use every 2 hours 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.

(ii) *For solid dosage forms, the product (lozenge or tablet) contains phenol or phenolate sodium equivalent to 10 to 50 milligrams phenol.* Adults and children 12 years of age and older: Allow the product (lozenge or tablet) to dissolve slowly in the mouth. May be repeated every 2 hours or as directed by a dentist or doctor. Children 6 to under 12 years of age: Allow product (lozenge or tablet) to dissolve slowly in the mouth. May be repeated every 2 hours, not to exceed 300 milligrams phenol in 24 hours, or as directed by a dentist or doctor. Children under 6 years of age: Consult a dentist or doctor.

(7) *For products containing salicyl alcohol identified in § 356.10(g)*—(i) *For dosage forms other than solid, the product is a 1- to 6-percent solution or suspension.* Adults and children 2 years of age and older: Apply to the affected area. Gargle, swish around, or allow to remain in place at least 1 minute and then spit out. Use up to 4 times daily 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 solid dosage forms, the product contains 50 to 100 milligrams salicyl alcohol.* Adults and children 2 years of age or older: Allow product to dissolve slowly in the mouth. May be repeated every 2 hours as needed or as directed by a dentist or doctor. Children under 2 years of age: Consult a dentist or doctor.

§ 356.65 Labeling of astringent drug products.

(a) *Statement of identify.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "oral astringent."

(b) *Indications.* The labeling of the product states, under the heading "Indications," the following: "For temporary relief of occasional minor irritation, pain, sore mouth, and sore throat."

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

(1) *For all products containing any ingredient identified in § 356.14.* "If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea, or vomiting, consult a doctor promptly. If sore mouth symptoms do not improve in 7 days, 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 alum identified in § 356.14(a), the product is a 0.2- to 0.5-percent aqueous solution.* Adults and children 2 years of age and older: Apply to the affected area. Gargle, swish around, or allow to remain in place at least 1 minute and then spit out. Use up to 4 times daily 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 zinc chloride identified in § 356.14(b), the product is a 0.1- to 0.25-percent aqueous*

solution. Adults and children 2 years of age and older: Apply to the affected area. Gargle, swish around, or allow to remain in place at least 1 minute and then spit out. Use up to 4 times daily 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.

§ 356.70 Labeling of debriding agent/oral wound cleanser drug products.

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

(b) *Indications.* The labeling of the product states, under the heading "Indications," either or all of the following:

(1) "Aids in the removal of phlegm, mucus, or other secretions associated with occasional sore mouth."

(2) "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."

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

(4) *Other allowable statements.* In addition to the required information specified in paragraphs (a), (b), (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 warnings under the heading "Warnings":

(1) *For all products containing any ingredient identified in § 356.16.* "Do not use this product for more than 7 days unless directed by a dentist or doctor. If sore mouth symptoms do not improve in 7 days; if irritation, pain, or redness persists or worsens; or if swelling, rash, or fever develops, see your dentist or doctor promptly."

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

(1) *For products containing carbamide peroxide identified in § 356.16(a), the product is a 10- to 15-percent solution in anhydrous glycerin—(i) For direct application.* Adults and children 2 years of age and older: 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 4 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 a mouthwash (oral rinse).* Adults and children 2 years of age and older: 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 4 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 § 356.16(b), the product is a 3-percent aqueous solution—(i) For direct application.* Adults and children 2 years of age and older: Apply several drops 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 4 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.* Adults and children 2 years of age and older: Mix with an equal amount of warm water. Swish around in the mouth over the affected area for at least 1 minute and then spit out. Use up to 4 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 bicarbonate identified in § 356.16(c).* Adults and children 2 years of age and older: Prepare a solution by mixing ½ to 1 teaspoon in ½ glass (4 ounces) of water. Swish around in mouth over affected area for at least 1 minute and then spit out. Use up to 4 times daily or as directed by a dentist or doctor. Children under 12 should be supervised in the use of the product. Children under 2 years of age: Consult a dentist or doctor.

(4) *For products containing sodium perborate monohydrate identified in § 356.16(d).* Adults and children 6 years of age and older: 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 or gargle for at least 1 minute and then spit it out. Do not swallow. Use up to 4 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. Consult a dentist or doctor for use in children under 6 years of age.

§ 356.75 Labeling of demulcent drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "oral demulcent."

(b) *Indications.* The labeling of the product states, under the heading "Indications," the following: "For temporary relief of minor discomfort and protection of irritated areas in sore mouth and sore throat."

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

(1) *For all products containing any ingredient identified in § 356.18.* "If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea, or vomiting, consult a doctor promptly. If sore mouth symptoms do not improve in 7 days, see your dentist or doctor promptly."

(2) *For products containing glycerin identified in § 356.18(c).* "Do not use full strength. Dilute with two or three volumes of water."

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

(1) *For products containing elm bark identified in § 356.18(a), the product is 10- to 15-percent elm bark in a solid dosage form.* Adult and children 2 years of age and older: Allow product to dissolve slowly in the mouth. May be repeated every 2 hours as needed or as directed by a dentist or doctor. Children under 2 years of age: Consult a dentist or doctor.

(2) *For products containing gelatin identified in § 356.18(b)—(i) For dosage forms other than solid, the product is a 5- to 10-percent solution or suspension containing a sufficient quantity of gelatin to form a semi-solid state.* Adults and children 2 years of age and older: Apply to the affected area. Gargle, swish around in the mouth, or allow to remain in place for at least 1 minute and then spit out. Use as needed 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.

(ii) *For solid dosage forms, the product contains a sufficient quantity of gelatin to form a solid state.* Adults and children 2 years of age and older: Allow product to dissolve slowly in the mouth. May be repeated as needed or as directed by a dentist or doctor. Children under 2 years of age: Consult a doctor.

(3) *For products containing glycerin identified in § 356.18(c).* Adults and children 2 years of age and older: Apply a solution containing glycerin diluted with 2 or 3 parts of water to the affected area. Gargle, swish around in the mouth, or allow to remain in place for at least 1 minute and then spit out. Use as needed 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.

(4) *For products containing pectin identified in § 356.18(d)*—(i) *For dosage forms other than solid, the product is a solution or a gel containing a sufficient quantity of pectin to form a semi-solid state.* Adults and children 2 years of age and older: Apply to the affected area. Gargle, swish around in the mouth, or allow to remain in place for at least 1 minute and then spit out. Use as needed 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.

(ii) *For solid dosage forms, the product contains a sufficient quantity of pectin to form a solid state.* Adults and children 2 years of age and older: Allow product to dissolve slowly in the mouth. May be repeated as needed or as directed by a dentist or doctor. Children under 2 years of age: Consult a dentist or doctor.

§ 356.78 Labeling of combination drug products.

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

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

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

(1) *For permitted combinations identified in § 356.20(e).* The indications in § 341.85 should be used. (To be published in a future issue of the **Federal Register**.)

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

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

§ 356.80 Professional labeling.

(a) The labeling of products containing oral anesthetic/analgesic active ingredients identified in § 356.10 provided to health professionals (but not to the general public) may contain the following indication: "For the temporary relief of pain associated with" (select one or more of the following conditions: "tonsilitis," "pharyngitis," "throat infections," or "stomatitis.")

(b) The labeling of products containing oral debriding agent/oral wound cleanser active ingredients identified in § 356.16 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)."

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

4. The authority citation for 21 CFR Part 369 continues to read as follows:

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

§ 369.20 [Amended]

5. In subpart B, § 369.20 *Drugs; recommended warning and caution statements* is amended by removing the entries for "SODIUM PERBORATE MOUTHWASH AND GARGLE AND TOOTHPASTE" and "THROAT PREPARATIONS FOR TEMPORARY RELIEF OF MINOR SORE THROAT: LOZENGES, TROCHES, WASHES, GARGLES, ETC."

Dated: October 5, 1987.

Frank E. Young,

Commissioner of Food and Drugs.

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