DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 356 and 369

[Docket No. 81N-0033]

RIN 0905-AA06

Oral Health Care Drug Products for Over-the-Counter Human Use; Amendment to Tentative Final Monograph to Include OTC Relief of Oral Discomfort Drug Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking amending the tentative final monograph (proposed rule) for over-the-counter (OTC) oral health care drug products by adding the conditions for which OTC relief of oral discomfort drug products are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products and public comments on the advance notice of proposed rulemaking (published in the **Federal Register** of May 25, 1982; 47 FR 22712) to establish 21 CFR part 354 and after considering the tentative final monograph on OTC oral health care drug products (published in the **Federal Register** of January 27, 1988; 53 FR 2436). This proposal incorporates the rulemaking for OTC relief of oral discomfort drug products 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 January 22, 1992. Written comments, objections, or requests for oral hearing on the combination of potassium nitrate and an anticaries active ingredient, identified in proposed § 356.26(h), by November 25, 1991. 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. The agency is requesting comments and objections regarding proposed § 356.26(h) within a 60-day period so that the marketing status of a combination drug product containing potassium nitrate and an anticaries active ingredient can be determined in an expeditious manner. New data by September 24, 1992. Comments on the new data by November 24, 1992. Written comments on the agency's economic impact determination by January 22, 1992.

ADDRESSES: Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-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 the 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 the **Federal Register** of July 30, 1982 (47 FR 32953), in response to a request for an extension of time, the comment period and reply comment period for OTC oral health care drug products were extended to November 22, 1982 and to December 22, 1982, respectively. In the **Federal Register** of December 28, 1982 (47 FR 57739), the reply comment period was extended to January 21, 1983.

The first part of the agency's proposed regulation, in the form of a tentative final monograph for OTC oral health care (anesthetic/analgesic, astringent, debriding agent/oral wound cleanser, and demulcent) drug products was published in the **Federal Register** of January 27, 1988 (53 FR 2436).

In the **Federal Register** of May 25, 1982 (47 FR 22712), 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 relief of oral discomfort drug products, together with the recommendations of the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products (Dental 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 the **Federal Register** of July 30, 1982 (47 FR 32952), in response to a request for an extension of time, the comment period and reply comment period for OTC relief of oral discomfort drug products were extended to October 22, 1982 and to November 22, 1982, respectively.

In accordance with § 330.10(a)(10), the data and information considered by the Dental Panel were placed on public display in the Dockets Management Branch (address above), after deletion of a small amount of trade secret information.

In response to the advance notice of proposed rulemaking on OTC relief of oral discomfort drug products, one drug manufacturers' association, one professional association, one consumer group, nine drug manufacturers, and two health care professionals submitted comments. Copies of the comments received are on public display in the Dockets Management Branch (address above) under Docket No. 80N-0228 and will be incorporated into Docket No. 81N-0033.

The Dental Panel was charged to review and evaluate dental and dental care drug products including agents for oral mucosal injury and agents for the relief of oral discomfort. Oral mucosal injury drug products are OTC preparations intended to relieve oral soft tissue injury by cleansing or promoting the healing of minor oral wounds or irritations (48 FR 33984). Agents for the relief of oral discomfort are OTC preparations to treat minor trauma or irritations of a transient nature to the gums or teeth (47 FR 22712 at 22717). The Oral Cavity Panel was charged to evaluate ingredients in OTC preparations intended for use for the temporary relief of symptoms due to minor irritations, inflammations, and other lesions of the mucous membranes of the oral cavity (47 FR 22760 at 22765). Because of the overlap between the rulemaking on OTC oral mucosal injury drug products and the rulemaking on OTC oral health care drug products, the agency incorporated that part of the oral mucosal injury rulemaking that includes oral wound cleansers into the tentative final monograph for OTC oral health care drug products published in the **Federal Register** of January 27, 1988 (53 FR 2436). Likewise, because the ingredients reviewed as relief of oral discomfort agents and the ingredients

reviewed as oral health care drug products are indicated for similar therapeutic purposes in the same area (i.e., the oral cavity), in this document, the agency is proposing to combine the two rulemakings into the rulemaking on OTC oral health care drug products (21 CFR part 356). Accordingly, the advance notice of proposed rulemaking to establish 21 CFR part 354 is being merged into the rulemaking to establish 21 CFR part 356. The intent of the combined rulemaking is to identify those ingredients that are generally recognized as safe and effective in temporarily relieving the symptoms associated with minor oral wounds or other irritations of the mouth, gums, or teeth. Combining these two rulemakings into one will result in more consistent labeling on these OTC drug products intended for topical use in the oral cavity and in less confusion for the manufacturers of these drug products and for the consumer.

FDA is issuing the tentative final monograph for OTC oral health care drug products in several segments. This document amends the first segment that addressed OTC oral health care anesthetic/analgesic, astringent, debriding agent/oral wound cleaner, and demulcent drug products (published in the **Federal Register** of January 27, 1988; 53 FR 2436). A subsequent segment of the tentative final monograph on OTC oral health care drug products 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. This segment will be published in a future issue of the **Federal Register**. Another segment will address comments received in response to the advance notice of proposed rulemaking that results from the agency's call-for-data for antiplaque ingredients published in the **Federal Register** of September 19, 1990 (55 FR 38560).

The advance notice of proposed rulemaking, which was published in the **Federal Register** on May 25, 1982 (47 FR 22712), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the present document is designated as a "tentative final monograph." In this tentative final monograph (proposed rule) to amend part 356 (proposed in the **Federal Register** of January 27, 1988; 53 FR 2436), FDA states for the first time its position on the establishment of a monograph that includes OTC relief of oral discomfort drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC oral health care drug products and will include relief of oral discomfort drug products.

This proposal constitutes FDA's tentative adoption of the Dental Panel's conclusions and recommendations on OTC relief of oral discomfort drug products, as modified on the basis of the comments received and the agency's independent evaluation of that report. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above) either under Docket No. 80N-0228 or 81N-0033. All information on file under Docket No. 80N-0228 is being incorporated into Docket No 81N-0033. These modifications are reflected in the following summary of the comments and FDA's responses to them.

The OTC drug 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 relief of oral discomfort drug products (47 FR 22712), 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** and that the conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of whether further testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 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 a further delay in having a new product available for manufacture.

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss, but also interfere with consumers' access to these 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 January 30, 1973 (38 FR 2781) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking for OTC relief of oral discomfort drug products. The volumes are on public display in the Dockets Management Branch (address above).

I. The Agency's Tentative Conclusions on the Comments

A. General Comments on Relief of Oral Discomfort 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 at 9471 to 9472) and in paragraph 3 of the preamble to the tentative final monograph for OTC antacid drug products, published in the **Federal Register** of November 12, 1973 (38 FR 31260). FDA reaffirms the conclusions stated in those documents. Court decisions have confirmed the agency's authority to issue substantive regulations by rulemaking. (See, e.g., *National Nutritional Foods Association* v. *Weinberger*, 512 F.2d 688, 696–698 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers* v. *FDA*, 487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd*, 637 F.2d 887 (2d Cir. 1981).)

2. One comment was vitally concerned about certain aspects of the Dental Panel's report and recommended monograph because, if these recommendations are adopted as substantive rulemaking, the firm's ability to stay in business would be drastically affected. Although agreeing that OTC drugs should be generally recognized as safe and effective and not misbranded, the comment was concerned that the direction taken by that Panel and the agency would eliminate competitive differences between OTC drug products available in the marketplace. The comment argued that these differences, which appear small and inconsequential by scientific standards, are of vital importance to the consumer and also help maintain our economic system. The comment further argued that any system of review that forces all marketed products to be equal in composition and claims is to the advantage of firms that can afford to do the most advertising.

The comment named four of its OTC drug products that would be affected by the Dental Panel's recommendations and stated that these four products represent about two-thirds of the company's total sales. The comment stated that, if required, these four drug products could be reformulated and relabeled, but at an increased cost to the company as well as to the consumer. The comment added that it would be prepared to document these costs at the appropriate time. The comment claimed that, unlike larger companies, its firm is not equipped to do product testing and that it is not easy to get dental people or dental schools to perform tests at a reasonable price on products such as those manufactured by the company.

In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of the combined economic impacts of the entire OTC drug review. Based on this assessment, the agency has determined that no OTC drug review rule, including this proposed rule on drug products for the relief of oral discomfort, is a major rule as defined by Executive Order 12291. Nor is any one OTC drug review rule likely to have a significant economic impact on a substantial number of small entities, as defined in the Regulatory Flexibility Act. 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. However, the assessment did recognize the possibility that some individual monographs might have a significant impact on small firms. Therefore, the assessment included a discretionary regulatory flexibility analysis that identified ways of reducing burdens on small firms. The agency invited public comment in the advance notice of proposed rulemaking (47 FR 22712) regarding any impact this rulemaking would have on OTC drug products for the relief of oral discomfort. Comments were to be accompanied by appropriate documentation. Although comments were received on this matter, no documentation was submitted with this or other comments that would alter the determination reached by the agency in the economic assessment that there is no legal basis for any preferential waiver, exemption, or tiering strategy for small firms compatible with the public health requirements of the Federal Food, Drug, and Cosmetic Act (the act). In this proposal the agency is again inviting public comment on the economic impact of the rule.

The agency recognizes that some changes in the current manufacturing and marketing practices of OTC drug products for the relief of oral discomfort may result if the Dental Panel's recommendations are fully implemented. In reformulating a number of OTC drug products for the relief of oral discomfort to comply with the final monograph, there will be fewer active ingredients used and, consequently, some of the differences among these products will disappear from the marketplace. However, some product differences in active and inactive ingredients will remain. In addition, under the agency's revised labeling policy for OTC drug products, some labeling variations concerning claims will be allowed. (See comment 12 below.) Firms will continue to be permitted to market competitive OTC drug products for the relief of oral discomfort that either comply with the conditions of the monograph or are the subject of an approved new drug application.

3. One comment objected to the Dental Panel's recommendation that beeswax should not be included as an inactive ingredient in products intended for use in an open tooth cavity for the relief of toothache (47 FR 22712 at 22726). The comment contended that the Panel's position that beeswax, because of its occlusive properties, exposes the consumer to unnecessary risks was based on opinion and not on data. The comment added that the Panel was not charged with reviewing inactive ingredients and that, instead of condemning beeswax, the Panel should have expressed its concern and recommended that a study of occlusivity be conducted.

The comment submitted many consumer letters and two in vitro studies in support of the safety of beeswax as an inactive ingredient in toothache relief products (Ref. 1). The consumer letters contained complaints about the reformulation of a toothache product from one that contains beeswax to one that conforms to the Dental

Panel's recommendations and does not contain beeswax. The comment stated that consumer response to the reformulated product was highly unfavorable, unlike the almost completely favorable response to the beeswax formulation. The product was subsequently reformulated to the beeswax formulation in order to maintain this product on the market.

The first submitted study involved an apparatus for measuring the in vitro transfer of air pressures of 25, 50, 75 and 100 millimeters of mercury from the apex of the tooth, through a root canal that was packed with cotton, to an open tooth cavity that was packed with "toothache gum" containing beeswax. The purpose was to show that the gum formulation does not hinder the transfer of gas pressure and therefore is not occlusive. The second in vitro study was designed to measure the ability of C^{14}-glucose in an artificial saliva mixture to migrate from the bottom of a tooth cavity through "toothache gum" containing beeswax that was packed into the tooth cavity. The comment stated that the results of the studies show that beeswax does not hinder the flow of soluble materials into and out of tooth cavities and, except at very low pressures, does not hinder the transfer of gas pressure. The comment contended that these studies demonstrating the safety of using a "toothache gum" containing beeswax in an open tooth cavity negate the Panel's "opinion" that beeswax would prevent the escape of gases and fluids from a degenerating pulp.

The agency agrees with the Dental Panel that it is inappropriate to use inactive ingredients that will form an occlusive barrier in drug products for the relief of toothache in an open tooth cavity. The Panel believed, and the agency concurs, that any occlusive agent such as beeswax should not be included in such products because "the use of occlusive agents * * * in a tooth cavity * * * exposes the consumer to unnecessary safety risks." The Dental Panel reasoned that "any agent which acts as a physical barrier and does not permit the escape of fluids and gases from a degenerating pulp * * * may result in increased pain and possible spread of infection." (See 47 FR 22712 at 22726.)

The agency finds that the submitted in vitro data described above cannot be extrapolated to a vital or partially vital tooth set in a bony socket surrounded by soft tissue in an otherwise healthy patient where the bacterial flora of the saliva is constantly changing. Therefore, in the agency's judgment the submitted data are inadequate to support the safety of including beeswax as an inactive ingredient in drug products for the relief of toothache. The agency concludes that in this situation clinical studies are necessary to demonstrate safety and effectiveness of the product. Such studies could be very short in duration.

The OTC drug review is an active, not an inactive, ingredient review, and the Dental Panel's recommendations concerning inactive ingredients in toothache relief drug products are not included in this document. However, agency regulations in § 330.1(e) (21 CFR 330.1(e)) state that one of the conditions under which OTC drug products are generally recognized as safe and effective is that the product contain "only suitable inactive ingredients which are safe * * * and do not interfere with the effectiveness of the preparation." The agency is concerned that occlusive inactive ingredients such as beeswax may compromise the safe use of products for the relief of toothache not only because they may prevent the escape of fluid and gases from a degenerating tooth pulp, but also because they can form temporary fillings that would encourage the consumer to significantly delay treatment by a dentist.

To support this position, the agency notes that several of the consumer complaints about the comment's reformulation of its product to one that does not contain beeswax were based on the consumer's inability to use the product to delay or completely avoid seeking professional help in resolving the underlying condition that caused the toothache. The agency believes that a toothache relief product in a dosage form that lends itself to the formation of a temporary filling that allows a consumer to self-treat an open tooth cavity on a long-term basis provides an unwarranted opportunity for consumers to misuse such products. In regulating drug products for the relief of toothache that are subject to the final monograph, the agency will consider whether beeswax, or any other inactive ingredient that lends itself to the formation of a temporary filling, compromises the safe use of toothache products by preventing the escape of fluid and gases from a degenerating tooth pulp. If the agency makes such a determination, appropriate regulatory action will be taken.

The agency's comments and evaluation of the data are on file in the Dockets Management Branch (address above) (Ref. 2).

References

(1) Comment No. C00006, Docket No. 80N-0228, Dockets Management Branch.

(2) Letter from W.E. Gilbertson, FDA, to B.L. Pritz, Grandpa Brands Company, coded LET17, Docket No. 80N-0228, Dockets Management Branch.

B. Comments on Specific Relief of Oral Discomfort Drug Products

4. One comment from a professional association stated that the association recognizes the use of benzocaine and butacaine sulfate as safe and effective for OTC use as analgesics for the oral mucosa, but does not recognize the effectiveness of phenolic preparations for that use.

The association's view of benzocaine and butacaine sulfate for use as oral mucosal analgesics is in agreement with the Dental Panel's Category I recommendation (47 FR 22712 at 22757 to 22758). The Dental Panel concluded that penolic preparations of 0.25 to 1.5 percent phenol and phenolate sodium, if used as directed, are safe and effective as oral mucosal analgesics for the relief of oral discomfort (47 FR 22739 to 22740). The Oral Cavity Panel also reviewed 0.5 to 1.5 percent phenol and phenolate sodium (47 FR 22760 at 22814 to 22815) and recognized the safety and effectiveness of these ingredients as OTC anesthetic/analgesics for topical use on the mucous membranes of the mouth and throat.

In this amendment, the agency is proposing to include oral mucosal analgesics in the anesthetic/analgesic therapeutic category proposed in the first segment of the tentative final monograph for OTC oral health care drug products. (See Part II. paragraph B.5. below.) The ingredients and labeling for oral health care anesthetic/analgesics included in this amendment reflect the agency's evaluation of both Panels' recommendations.

After evaluating both Panels' recommendations regarding the effectiveness of phenol for topical use on the mucous membranes of the mouth and throat, the agency concurs with the Panels' conclusions that phenol is an effective oral mucosal analgesic. Further, the comment did not submit any data or other information to support its position that phenol is not effective as an oral mucosal analgesic nor did it offer any criticism of the data used by the Panel to support the effectiveness of phenol as an oral mucosal analgesic.

The Dental Panel recommended a phenol concentration range of 0.25 to 1.5 percent for use as an oral mucosal analgesic, whereas the Oral Cavity Panel recommended 0.5 to 1.5 percent

for anesthetic/analgesic drug products. Based on the available information concerning OTC drug products containing phenol, the agency is proposing that the minimum concentration of phenol for use as an oral mucosal analgesic be 0.5 percent rather than 0.25 percent for the following reasons: (1) The data reviewed by the Dental Panel concerning 0.25 percent phenol consist of a study that only lists 0.25 percent phenol in a table of topical anesthetic drugs "which were partially or totally ineffective" as providing "numbness (incomplete)" in clinical testing that involved the application of a painful electrical stimulus to the tip of the tongue (Ref. 1), and (2) other references state that phenol possesses topical anesthetic activity at a concentration of 0.5 percent (Refs. 2 and 3). Therefore, the agency concurs with the Oral Cavity Panel's recommendation and is proposing in this amendment that the concentration range of phenol used as an oral mucosal analgesic be 0.5 to 1.5 percent.

For teething preparations, however, the agency is proposing to limit the concentration to 0.5 percent phenol because no data for other concentrations of teething preparations were submitted to the Dental Panel or to the agency. Because the first segment of the tentative final monograph for OTC oral health care drug products did not address teething preparations, the agency is including directions for use of teething preparations in § 356.52(d)(7)(iii) of this amendment. (See comment 36 below.)

References

(1) Adriani, J., et al., "The Comparative Potency and Effectiveness of Topical Anesthetics in Man," *Clinical Pharmacology and Therapeutics*, 5:49–62, 1964.

(2) "AMA Drug Evaluations—1980," 4th Ed., American Medical Association, Chicago, p. 1022, 1980.

(3) Martindale, W., "The Extra Pharmacopeia," 26th Ed., The Pharmaceutical Press, London, p. 202, 1972.

5. Three comments objected to the Dental Panel's recommendation that benzocaine be placed in Category III as an agent for the relief of toothache. All of the comments referred to a recent published study in which benzocaine was tested as an agent for the temporary relief of toothache, and each comment contained a short summary of the results of this study (Ref. 1). Two of the comments felt that the data submitted to the Panel in support of the effectiveness of benzocaine as a toothache remedy were better than the data for eugenol, which the Panel placed in Category I.

One comment believed that there was a discrepancy between the standard of effectiveness used to evaluate eugenol and the standard used to evaluate benzocaine and other ingredients. The comment stated that the Panel did not provide any reason why benzocaine is not an effective toothache relief agent, but simply stated that "there are insufficient data to establish effectiveness of benzocaine after application into a tooth cavity, as an agent for the relief of toothache, at the 2- to 20-percent concentrations" (47 FR 22712 at 22730). The comment contended that the amount of evidence in its submissions to the Panel (Refs. 2, 3, and 4) was sufficient to support the effectiveness of benzocaine and requested that the agency place benzocaine in Category I as an agent for the relief of toothache pain, based on these submissions and the additional study by Sveen, Yaekel, and Adair (Ref. 1). One comment felt that the data in support of benzocaine as a toothache relief agent in a gel dosage form should be extended to benzocaine in a poultice dosage form. The comment felt that in the absence of evidence to the contrary, a poultice should deliver the drug as well, if not better than a gel, because it will not wash away easily with saliva. A fourth comment agreed with the Panel's Category III categorization of benzocaine preparations based on the lack of efficacy data.

The agency has reviewed the effectiveness data on eugenol (Refs. 5 through 9) that were submitted to the Dental Panel and has determined that the data are insufficient to place eugenol in Category I as a toothache remedy (see comment 7 below). Therefore, in this tentative final monograph the agency is proposing that eugenol be classified in Category III as an agent for the relief of toothache.

The agency has also reviewed the comment's data plus other data (Refs. 2, 4, 5, 6, and 10 through 14) submitted to the Panel in support of the effectiveness of benzocaine as an agent for the relief of toothache and agrees with the Panel's Category III classification. The submissions contained data from animal studies that showed benzocaine to be a safe and effective topical anesthetic. However, there were no clinical data to demonstrate benzocaine's effectiveness in reducing pain due to a cavity in a tooth. The data submitted to the Panel were sufficient to establish benzocaine as a Category I oral mucosal analgesic, but inadequate to establish its effectiveness as an agent for the relief of toothache.

The agency has reviewed the study by Sveen, Yaekel, and Adair (Ref. 1), cited by three of the comments as evidence of the effectiveness of benzocaine, and concludes that it does not provide sufficient evidence to reclassify benzocaine to Category I as an agent for the relief of toothache. In the study, 49 patients who had a toothache resulting from dental caries were given either a gel dosage form containing 7.5 percent benzocaine or a placebo gel without any medication. Of the 24 patients receiving the gel containing benzocaine, 20 (83 percent) were reported to be relieved of pain with an average onset time of 3.7 minutes. The placebo gel gave relief to 16 percent of the 25 patients who received it.

One of the major problems with this study involves the inadequate documentation of efficacy measurements, i.e., the rating scales used to measure pain intensity and relief are not defined. No details are given of the actual scales used by the investigator to determine the pain intensity or the period of time that actual relief was experienced. The results only indicate that relief or no relief was obtained. Paragraph 6 of the methods and materials section of this study indicates that the data were collected by an investigator who visually examined the patient's tooth, applied the benzocaine or placebo gel to the tooth and surrounding gingiva, and filled in the patient record form recording any changes in the relief of the toothache. However, no details are given of the actual scales used to measure baseline pain intensity or pain relief, e.g., visual analog scales or rating scales for pain intensity and pain relief. Assuming a 2-point pain relief category scale, as implied by Table II (Ref. 1), the actual relief experienced could have been trivial (slight relief) to substantial (complete relief). Additionally, the details regarding the duration of pain relief are inadequate. For the placebo group, the investigator mentioned that some subjects experienced pain relief for 1 or 2 minutes, and four patients felt pain relief for more than 10 minutes. For the benzocaine group, however, the investigator did not determine the duration of pain relief at all.

Another problem is the lack of assurance that levels of pain and other patient characteristics affecting a response were comparable between the test and control groups at baseline. The article did not compare the two treatment groups for baseline pain intensity and for use of aspirin, codeine, or other analgesic medications. It is possible that the difference between treatment groups regarding pain relief is attributable to differences between the

two groups in baseline levels of these two factors. It is important that the control and test groups have comparable levels of pain severity at baseline because the degree of pain relief is usually correlated with initial pain intensity.

The randomization procedure for the distribution of the medication was unorthodox. It consisted of the investigator randomly selecting a tube of medication from a box containing an equal number of active and placebo tubes. This procedure is subject to possible bias by the investigator, especially if the contents of the tubes were not carefully disguised. Any knowledge of the identity of the specific medication that a given patient has received would have likely influenced the investigator's collection of data from the patient, and hence made the evidence much weaker. The use of a random number list or card-shuffling technique to assign medication in a random fashion to consecutively recruited patients would have been simple and scientifically more desirable.

Under the results section (paragraph 4) of this study (Ref. 1), it is indicated that some subjects disliked the taste of "the applied substance." It is conceivable that the benzocaine may have imparted a distinctive taste to the gel that would have enabled both the patient and the investigator to identify the tubes of medication containing active drug. This would invalidate the results of this study, especially in light of the randomization procedure used.

In summary, the results of this study, as summarized in Table II (Ref. 1), provide some evidence for a pain-relieving effect for benzocaine gel when applied as described in the article. The study design, however, was flawed and as a result the study is not adequate to support the reclassification of benzocaine from Category III to Category I as an agent for the relief of toothache. The two most critical problems with this published study involve the poor documentation of efficacy measurements, e.g., the absence of scales for determining pain relief and duration of relief, and the lack of assurance that levels of pain and other patient characteristics affecting the response were comparable in the two groups at baseline. In any future studies, the nature of the scales used and the patients' reports of relief should be well defined in order to determine the magnitude of the clinical effect. The "blindness" of the study should be clarified by examination of the taste of benzocaine gel in comparison to its vehicle.

Based on its review of data submitted to the Dental Panel and the article by Sveen, Yaekel, and Adair (Ref. 1) submitted with the comments, the agency is classifying benzocaine in Category III as an agent for the relief of toothache in this amendment. If additional data from well-designed clinical studies that show benzocaine to be an effective toothache pain remedy are received, the agency will consider reclassifying benzocaine in Category I as an agent for the relief of toothache. At that time, the acceptable dosage forms for benzocaine would be determined.

References

(1) Sveen, O.B., M. Yaekel, and S.M. Adair, "Efficacy of Using Benzocaine for Temporary Relief of Toothache," Oral Surgery, Oral Medicine, Oral Pathology, 53:574–576, 1982.
(2) OTC Volume 080048.
(3) OTC Volume 080114.
(4) OTC Volume 080255.
(5) OTC Volume 080003.
(6) OTC Volume 080081.
(7) OTC Volume 080034.
(8) Summary Minutes of the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products, 5th Meeting, October 10 and 11, 1973, in OTC Volume 08APA2.
(9) Summary Minutes of the Advisory Review Panel of OTC Dentifrice and Dental Care Drug Products, 14th Meeting, October 16 and 17, 1974, in OTC Volume 08APA2.
(10) OTC Volume 080017.
(11) OTC Volume 080055
(12) OTC Volume 080191.
(13) OTC Volume 080214.
(14) OTC Volume 080258.

6. One comment noted that its submissions of data to the Dental Panel concerning products containing water-soluble chlorophyllin are listed in the Panel's report under the heading "Submissions by Firms" (47 FR 22712 at 22714), but that water-soluble chlorophyllin is not mentioned in the report. The comment stated that although chlorophyllin has been classified primarily as a wound healing agent, its mode of action has not been conclusively defined and the literature indicates that it produces beneficial effects not necessarily explainable by its wound-healing properties. According to the comment, dental and medical reports consistently refer to relief of discomfort as a result of topical administration of chlorophyllin and, in this capacity, the ingredient is acting as an analgesic in that it produces a lessening of sensibility to pain.

The comment contended that the Dental Panel defined "analgesic" so narrowly that the definition excludes chlorophyllin as well as other pain relievers such as aspirin and adrenocorticosteroid hormones. Stating that the Panel defined an "analgesic (topical)" as "an ingredient used in drug products for surface application to provide temporary relief of discomfort by an anesthetic or analgesic effect" (47 FR 22716), the comment argued that the Panel dealt solely with ingredients with an anesthetic effect and did not include any ingredients with an "analgesic" effect in its review.

The comment added that a broader interpretation of what constitutes a topical analgesic is contained in the advance notice of proposed rulemaking for OTC external analgesic drug products, which reads: "Some drugs exert analgesic effects by eliminating a painful stimulus. These agents reduce swelling of the tissues or they neutralize noxious chemical substances that are released by trauma, an infection, or another process" (44 FR 69768 at 69777). The comment believed that the drugs so described could include chlorophyllin because the clinical studies submitted indicate that chlorophyllin provides patients with relief of oral discomfort. The comment concluded by requesting that water-soluble chlorophyllin be included in a broadened category of "oral mucosal analgesics" or in an added category of "miscellaneous agents for the relief of oral discomfort" so as to ultimately achieve Category I status.

The agency acknowledges that the comment did submit data regarding water-soluble chlorophyllin to the Dental Panel for review and that, although submissions concerning chlorophyllin are listed in the Panel's report on OTC drug products for the relief of oral discomfort, this ingredient is not discussed in that document. Because the data in the submissions dealt primarily with the wound-healing effects of chlorophyllin, it appears that the Panel reviewed this ingredient only as an oral wound-healing agent in its report on OTC oral mucosal injury drug products (published in the **Federal Register** of November 2, 1979; 44 FR 63270 at 63286). Reference to the comment's submissions in the list of submissions appearing in the relief of oral discomfort drug products report appears to have been an error that occurred as a result of the Panel's one large report subsequently being subdivided into three separate reports (i.e., anticaries, oral mucosal injury, and relief of oral discomfort).

The agency does not agree with the comment that the Dental Panel's definition of "analgesic" is so narrow that it would exclude pain relievers such as aspirin and adrenocorticosteroid hormones. The Panel's discussion of oral

mucosal analgesics (47 FR 22712 at 22736) did not include those pain relievers because no data were submitted to the Panel regarding the use of such drugs as oral mucosal analgesics. Because the Dental Panel's definition of "analgesic" is broad enough to include any analgesic ingredient regardless of its mechanism of action, the agency does not see any reason to change that definition.

The agency agrees with the statement in the external analgesic drug products report that "some drugs exert analgesic effects by eliminating a painful stimulus. These agents reduce swelling of the tissues or they neutralize noxious chemical substances that are released by trauma, an infection, or another process" (44 FR 69768 at 69777). However, the agency does not consider the submitted data adequate to demonstrate that chlorophyllin is an analgesic that acts in this manner. The data contain little information on the analgesic effect of chlorophyllin (Ref. 1). The data consist of many studies on the wound-healing effects and deodorizing properties of chlorophyllin, but only part of one article in the submissions deals with the analgesic effect of chlorophyllin (Ref. 2). That article contains a number of summarized clinical reports in which patients with various dental problems, e.g., extractions, gingivitis, stomatitis, and pyorrhea, were treated with a chlorophyllin preparation. The studies were conducted primarily to evaluate the healing effect of chlorophyllin; however, some observations were made regarding chlorophyllin's effect on pain.

The agency finds the clinical reports inadequate to demonstrate the analgesic effectiveness of chlorophyllin because there are insufficient details regarding the study designs; no information is given as to how or under what conditions the studies were conducted; the studies were not well-controlled or blinded; there was no recorded measurement of the condition of the subjects at baseline; and no information was given as to how relief of pain was evaluated. Therefore, in this amendment, the agency is not including chlorophyllin in an added category of "miscellaneous agents for the relief of oral discomfort," but is proposing that water-soluble chlorophyllin be classified as a Category III ingredient for use as an oral mucosal analgesic.

References

(1) OTC Volumes 080043 and 080168.

(2) Taraporvala, P.V., "A Preliminary Report on Therapy with Chlorophyll (Chloresium) in Dentistry," Journal of the Indian Medical Profession, 4:1905–1911, 1957.

7. One comment agreed with the Dental Panel's decision to place eugenol in Category I as an agent for the relief of toothache. Three other comments questioned the Panel's decision to place eugenol in Category I for this use. One of the comments stated that the Panel was apparently aware of the capacity of eugenol to damage viable tooth pulp when it advised that eugenol should be recommended only when there is "persistent, throbbing pain," because intermittent pain might "indicate that the pulp is still viable, and eugenol may compromise the pulp vitality in that case" (47 FR 22712 at 22728). The comment stated that a lay person with a toothache might not be readily able to distinguish the intermittent pain of a viable tooth; thus, eugenol has the potential for harmful effects unless used under professional supervision, is not an appropriate product for self-medication, and should not be permitted for OTC sale. Another comment contended that there was a danger with eugenol in that consumers may misuse it, in spite of adequate warnings on the label, by applying it in an open cavity from which a filling has been lost. The comment stated that because it is known that eugenol is an irritant, one cannot be assured that this problem can be avoided.

Two of the comments questioned the effectiveness data that the Dental Panel accepted for eugenol. One comment noted that the Panel stated that well-controlled, published studies on the effectiveness of eugenol for the relief of toothache are not available, and that the Panel considered the options of acknowledged experts in endodontics, who, however, did not agree with each other on the advisability of making eugenol available to the consumer as an OTC toothache remedy (47 FR 22728). The comment did not believe that the Panel's reliance on the opinion of experts in endodontics, as well as the published opinions of other experts that eugenol is a dental analgesic or has a topical anesthetic effect, is sufficient under OTC drug regulations (21 CFR 330.10(a)(4)(ii)) to establish the effectiveness of eugenol. The comment contended that the conflict of the expert opinion, as is evident from the Panel's own statement, should indicate that eugenol is not generally recognized as safe and effective and should not have been placed in Category I. The other comment contended that the Panel's Category I recommendation on eugenol was actually made with no data to prove effectiveness.

The agency has reviewed the information submitted to the Dental Panel (Refs. 1 through 5) and the data and information cited by the Panel (47 FR 22728) regarding the effectiveness of eugenol. The agency has determined that no data from any clinical studies involving eugenol were submitted to the Panel (47 FR 22728). The Panel recommended a Category I classification of eugenol for the following reasons: (1) The drug's long history of use in periodontal dressing and as a toothache remedy, (2) a belief that there is a need for an OTC toothache relief product for consumers, and (3) the opinion of an expert in endodontics that eugenol be retained for OTC toothache remedies (Ref. 4). A second expert called by the Panel stated that toothache remedies are basically not effective in correcting the cause of the toothache and only offer pain relief as a result of a placebo effect (Ref. 5). This expert questioned the consumer's ability to determine whether the toothache is of pulpal or periapical (dentinal) origin, i.e., whether there is irreversible damage to a tooth with a persistent, throbbing pain or reversible damage with a quick, sharp pain occurring as a response to stimuli such as heat or cold.

The agency does not find sufficient evidence to exist to establish general recognition of the effectiveness of eugenol as a toothache remedy within the requirements of the OTC drug regulations (21 CFR 330.10(a)(4)(ii)). There is a need for controlled clinical investigations that demonstrate the effectiveness of eugenol used for the relief of toothache. Therefore, the agency is reclassifying eugenol as an agent for the relief of toothache from Category I to Category III in this amendment.

References

(1) OTC Volume 080003.

(2) OTC Volume 080034.

(3) OTC Volume 080181.

(4) Summary Minutes of the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products, 5th meeting, October 10 and 11, 1973, OTC Volume 08APA2.

(5) Summary Minutes of the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products, 14th meeting, October 16, and 17, 1974, OTC Volume 08APA2.

8. Four comments cited a number of published studies (Refs. 1 through 10) to support the effectiveness of 5 percent potassium nitrate as a Category I tooth desensitizer. Some of these studies were cited in the Panel's report (Refs. 1 and 2); one was submitted to the Panel, but not cited in its report (Ref. 3); and one was submitted to the Panel, reviewed as unpublished data, and published subsequently (Ref. 4). Some of the

studies were published after the Panel completed its work and thus were not available to the Panel (Refs. 5 through 10). One comment cited five of these studies as the basis that a professional association used to recognize the usefulness and safety of a toothpaste containing 5 percent potassium nitrate for the relief of pain and discomfort from dentinal hypersensitivity (Refs. 1 through 4, and 9).

One comment requested that the Category III classification of 5 percent potassium nitrate be reexamined on the basis of the "file record" and the new data submitted by the comment (Ref. 11). The comment submitted two new clinical studies and copies of four clinical studies that were submitted by another comment (Ref. 12). The comment maintained that "substantial evidence, as defined in 21 U.S.C. 355, consisting of adequate and well-controlled investigations" clearly exists for a toothpaste containing 5 percent potassium nitrate in a compatible base. The comment maintained that no further studies on potassium nitrate are necessary because abundant clinical support is available to demonstrate the safety and effectiveness of potassium nitrate as a tooth desensitizing agent.

Another comment submitted five new, unpublished studies involving 254 subjects experiencing dentinal hypersensitivity (Ref. 12). The comment maintained that these studies demonstrate the effectiveness of 5 percent potassium nitrate in relieving dentinal sensitivity.

The agency has reviewed the data and concludes that there are sufficient data from two well-controlled clinical studies and three supportive studies to establish the effectiveness of 5 percent potassium nitrate as a tooth desensitizer.

In one study (Ref. 13), the effectiveness of two 5-percent potassium nitrate toothpastes was evaluated using methods recommended by the Dental Panel (47 FR 22712 at 22756 to 22757) in a placebo-controlled, 12-week, double-blind, 3-way parallel comparative study of 60 subjects. The hypersensitivity levels of the subject were assessed by two objective methods (i.e., thermal stimulus and tactile stimulus) and by subjective response. Reductions in tooth hypersensitivity caused by the two potassium nitrate dentifrices and by the placebo dentifrice (the dentifrice base without the potassium nitrate) were measured at the 2-week, 4-week, 8-week, and 12-week intervals. The reductions caused by the potassium nitrate dentifrices were compared statistically to the reductions caused by the placebo dentifrice at each time interval. When evaluated subjectively at 4 weeks, the two potassium nitrate dentifrices caused mean reductions in hypersensitivity of 42 and 41 percent, and the placebo dentifrice caused a mean reduction in hypersensitivity of 16 percent; at 8 weeks, the two potassium nitrate dentifrices caused mean reductions in hypersensitivity of 50 and 61 percent, and the placebo dentifrice caused a mean reduction in hypersensitivity of 23 percent; at 12 weeks, the two potassium nitrate dentifrices caused mean reductions in hypersensitivity of 75 and 69 percent, and the placebo dentifrice caused a mean reduction of 34 percent. When the decrease in hypersensitivity was assessed thermally by responses to a cold air blast (60 pounds per square inch (psi), 70 °F) from an air syringe, the two potassium nitrate dentifrices caused mean reductions in hypersensitivity of 46 percent (statistically significant) and 32 percent (not statistically significant) at 4 weeks, and the placebo caused a 27-percent reduction in hypersensitivity; at 8 weeks, the two potassium nitrate dentifrices caused mean reductions in hypersensitivity of 52 and 56 percent compared to a 33-percent reduction caused by the placebo; and at 12 weeks, the potassium nitrate dentifrices caused 74 and 70 percent reductions in mean hypersensitivity scores compared to a 48-percent reduction in hypersensitivity caused by the placebo. When the decreases in hypersensitivity were measured by responses to the tactile stimulation of a No. 23 dental probe, the two potassium nitrate dentifrices caused reductions in mean hypersensitivity scores of 46 and 52 percent at 4 weeks compared to the 24-percent reduction caused by the placebo; at 8 weeks, the two active ingredient dentifrices caused mean reductions of 72 and 67 percent, compared to the 36-percent reduction caused by the placebo; and at 12 weeks, the potassium nitrate products caused mean reductions of hypersensitivity of 87 and 82 percent compared to a 54-percent reduction caused by the placebo. Except where noted above, the reductions in tooth hypersensitivity caused by the active ingredient products were statistically significantly greater than the reductions caused by the placebo ($p. \leq .05$).

In a second study (Ref. 14), the effectiveness of a 5-percent potassium nitrate dentifrice and a 10-percent strontium chloride dentifrice were evaluated with a placebo in a 12-week, double-blind, 3-way comparative study of 45 subjects. The hypersensitivity responses were assessed by thermal stimulus and by subjective responses. Reductions in tooth hypersensitivity were measured at the 2-week, 4-week, 8-week, and 12-week intervals. When the decrease in mean hypersensitivity scores was assessed thermally by responses to a cold air blast (60 psi at 70 °F) from an air syringe, the potassium nitrate dentifrice caused a 31-percent reduction at 2 weeks compared to a 11-percent reduction caused by the placebo. The reduction in hypersensitivity assessed thermally and caused by the potassium nitrate dentifrice increased at each time interval to a 81-percent reduction in mean hypersensitivity scores at 12 weeks compared to a 14-percent reduction caused by the placebo. When the decrease in tooth hypersensitivity was assessed subjectively, the 5-percent potassium nitrate dentifrice caused a 34-percent reduction from baseline scores at 2 weeks, and the placebo caused a 4-percent reduction. This reduction in hypersensitivity caused by the potassium nitrate dentifrice increased at each interval to 79 percent at 12 weeks compared to a 32-percent reduction caused by the placebo dentifrice at 12 weeks. The 5-percent potassium nitrate dentifrice caused reductions in tooth hypersensitivity that were statistically significantly greater than the reductions caused by the placebo at all time intervals ($p \leq .05$).

In a third clinical study (Ref. 15), the desensitizing effect of a 5-percent potassium nitrate dentifrice was compared with a placebo dentifrice using a double-blind, placebo-controlled, 8-week study of 32 subjects. The subjects were restricted to individuals who complained of hypersensitivity following periodontal surgery. The hypersensitivity levels were assessed by measuring the subjects' response to a thermal stimulus (i.e., a 1-second blast of cold air, 60 psi, 70 °F± 3 °F) from an air syringe and by subjective evaluation. Subjectively, 78.6 percent of the subjects using the potassium nitrate dentifrice reported improvement at 4 weeks compared to 18.2 percent of the subjects using the placebo who reported improvement. At 8 weeks, 92.9 percent of the subjects using the potassium nitrate dentifrice reported improvement, and 54.5 percent of the subjects using the placebo reported improvement. When the decrease in mean hypersensitivity scores was assessed by measuring the responses to thermal stimulus, the potassium nitrate dentifrice caused a 57-percent decrease in hypersensitivity in 4 weeks. This decrease was significantly greater than the 32-percent decrease caused by the placebo ($p=.03$). At 8 weeks, although the 65-percent decrease in hypersensitivity caused by the

potassium nitrate dentifrice was not significantly greater than the 48-percent reduction associated with the placebo at the $p=.05$ level, it was significant at the $p=.1$ level and is thus supportive of effectiveness.

In addition to the above clinical studies of 8 or 12 weeks duration, two 4-week studies are supportive of the tooth desensitizing claim for 5 percent potassium nitrate (Refs. 4 and 16). In one study (Ref. 4), the effectiveness of a 5-percent potassium nitrate dentifrice was evaluated on 27 subjects in a double-blind, parallel, comparative study. Hypersensitivity levels were measured by the response to an electrical stimulus (pulp stethoscope), a thermal stimulus (cold air blast of 60 psi, 70 °F), and by subjective analysis. At 2 weeks, the potassium nitrate dentifrice caused a significantly greater desensitizing effect than the placebo ($p \leq .01$) for all three stimuli. This effect increased with continued use of the desensitizing agent during the 4 weeks of treatment and was consistently greater than the effect caused by the placebo ($p \leq .05$). Subjective data demonstrated that 92 percent of the subjects using the potassium nitrate dentifrice and 21 percent of the subjects using the placebo reported relief at the end of 4 weeks.

The other 4-week study (Ref. 16) was a double-blind, 3-way comparative, parallel study of 60 subjects that compared the effectiveness of a 5-percent potassium nitrate dentifrice, a 10-percent strontium chloride dentifrice, and a placebo dentifrice. Hypersensitivity levels were measured by the response to an electrical stimulus (pulp stethoscope), a thermal stimulus (cold air blast of 60 psi, 70 °F), and by subjective evaluation. After 2-weeks use and continuing through 4-weeks use, the 5-percent potassium nitrate dentifrice caused reductions in tooth hypersensitivity that were statistically significantly greater than the placebo reductions at all time intervals ($p < .05$). These results were observed for all three stimuli.

The agency is also aware of a 12-week, double-blind clinical study using 75 subjects in which the effectiveness of two commercially available 5 percent potassium nitrate dentifrices was compared to a placebo (Ref. 21). Hypersensitivity reduction was assessed by a thermal stimulus (1-second blast of cold air, 60 psi, 65 to 70 °F), a tactile stimulus (dental explorer No. 23), and by subjective evaluation. The scores from all three methods showed a gradual reduction in tooth sensitivity from baseline to each of the succeeding time intervals, but there were no statistically significant differences between either of the potassium nitrate dentifrices and the placebo.

Regarding the safety of potassium nitrate, the agency is aware that recent publications in the scientific literature have expressed concern that nitrates may be involved in the production of certain forms of cancer (i.e., gastric and liver cancer) when used at relatively low concentrations on a chronic basis (Refs. 17 through 20). Ingested nitrates can be converted in the oral cavity and the stomach to nitrites, which in turn can lead to endogenous nitrosation in the stomach; however, the extent and significance of the conversion of nitrate to nitrite in the body is not clear. Although, at this time, the data in the scientific literature do not justify changing the safety classification of potassium nitrate, the agency invites comments on this issue.

Based upon the evaluation of the available studies, the agency is proposing in this amendment to reclassify 5 percent potassium nitrate from Category III to Category I as a tooth desensitizer. Directions for using the dentifrice are discussed in comment 38 below.

The agency's detailed comments and evaluation of the data are on file in the Dockets Management Branch (Refs. 22 and 23).

References

(1) Hodosh, M., "A Superior Desensitizer—Potassium Nitrate," *Journal of the American Dental Association*, 88:831–832, 1974.

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(6) Council on Dental Therapeutics, "Desensitizing Dentifrice," Journal of the American Dental Association, 104:410, 1982.

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(9) Tarbet, W.J., et al., "An Evaluation of Two Methods for the Quantitation of Dentinal Hypersensitivity," Journal of the American Dental Association, 98:914–918, 1979.

(10) Tarbet, W.J., et al., "The Pulpal Effects of Brushing with a 5 Percent Potassium Nitrate Paste Used for Desensitization," Oral Surgery, Oral Medicine, Oral Pathology, 51:600–602, 1981.

(11) Comment No. C00011, Docket No. 80N–0228, Dockets Management Branch.

(12) Comment No. C00012, Docket No. 80N–0228, Dockets Management Branch.

(13) Axelrod, S., and S. Minkoff, "Desensitizing Dentifrice Study," draft of unpublished study, Comment No. C00011, Docket No. 80N–0228, Dockets Management Branch.

(14) Axelrod, S., and S. Minkoff, "Desensitizing Toothpaste, Long Term Safety and Effectiveness" (Study DDR 15–78), draft of unpublished study, Comment Nos. C00011 and C00012, Docket No. 80N–0228, Dockets Management Branch.

(15) Stolman, J., and G. Silverman, "Desensitizing Toothpaste, Post Periodontal Surgery-Hypersensitivity" (Study DDR 13–80), draft of unpublished study, Comment No. C00012, Docket No. 80N–0228, Dockets Management Branch.

(16) Goldman, P., and G. Silverman, "Desensitizing Toothpaste" (Study DDR 16–78), draft of unpublished study, Comment Nos. C00011 and C00012, Docket No. 80N–0228, Dockets Management Branch.

(17) Hartman, P.E., "Overview: Nitrate Load in the Upper Gastrointestinal Tract—Past, Present, and Future," Banbury Report 12: Nitrosamines and Human Cancer, 1982, Cold Spring Harbor Laboratory.

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(19) Mirvish, S.S., "The Etiology of Gastric Cancer," Journal of the National Cancer Institute, 71:631–647, 1983.

(20) Weisburger, J.H., "Role of Fat, Fiber, Nitrate and Food Additives in Carcinogenesis: A Critical Evaluation and Recommendations," Nutrition and Cancer, 8:47–62, 1986.

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(22) Letter from W.E. Gilbertson, FDA, to S. Most, Block Drug Company, Inc., coded LET008, Docket No. 80N–0228, Dockets Management Branch.

(23) Letter from W.E. Gilbertson, FDA, to D. Smith, Vicks Research Center, Richardson-Vicks Inc., coded LET009, Docket No. 80N–0028, Dockets Management Branch.

9. Two comments recommended that 10 percent strontium chloride be placed in Category I as a tooth desensitizing ingredient. The comments maintained that the effectiveness of 10 percent strontium chloride is supported by several adequate and well-controlled studies (Refs. 1 through 7), some of which were submitted to the Dental

Panel. One of these studies (Ref. 3) was submitted to the Panel as unpublished material and was published after the Panel was disbanded. One comment maintained that the Panel did not appear to challenge the design of the studies that were submitted, but rather questioned the results of the studies based upon the variability of the findings. The comment asserted that the variability was due to the different study designs utilized, as well as the known differences in individual responses to effective desensitizer dentifrice products. The comments also submitted a recently published study to support the effectiveness of strontium chloride as a tooth desensitizer (Ref. 8).

One of the comments submitted six additional clinical studies (Refs. 9 through 14) which have become available since the Panel disbanded. The comment mentioned that these new studies were conducted according to the Panel's recommended guidelines. The comment also submitted a statistical reanalysis of one of the studies submitted to the Panel (Ref. 15) and a statistical analysis of the combined data (Ref. 16) of two of the submitted clinical studies. In addition, the comment included testimonials from four experts who all stated that in their opinion, "* * * 10% strontium chloride hexahydrate in a desensitizing dentifrice is a safe and effective agent for the treatment of dentinal hypersensitivity" (Ref. 17). The comment maintained that "substantial evidence" as defined in 21 U.S.C. 355, "consisting of adequate and well-controlled investigations," clearly exists to support classification of 10 percent strontium chloride as a Category I tooth desensitizer.

A comment from a professional association concurred with the Dental Panel's Category III classification of strontium chloride as a tooth desensitizer. However, another comment, submitted to the agency at a later date, pointed out that on March 30, 1984, one commercially available 10-percent strontium chloride hexahydrate dentifrice was accepted by the association as a safe and effective desensitizing dentifrice (Ref. 18).

The agency has reviewed all of the submitted data and does not agree with the comments that the data are sufficient to classify strontium chloride in Category I as a tooth desensitizer. The agency agrees with the Panel's evaluation of the studies it reviewed (47 FR 22712 at 22755). The Panel stated that these studies were conflicting and inconclusive, and lacked early, consistent, favorable, and statistically significant results.

The statistical reanalysis by Wolf (Ref. 15), of a study that Uchida et al. (Ref. 3) had previously submitted to the Panel, compared the effectiveness of a 10-percent strontium chloride dentifrice to the effectiveness of a placebo dentifrice in relieving postperiodontal surgical hypersensitivity to mechanical stimuli, compressed air blast, and cold water. A subjective assessment of the degree of hypersensitivity for each stimulus was recorded. The published study by Uchida et al (Ref. 3) reported on data from 60 subjects, whereas the statistical reevaluation of the study by Wolf reported on data from 72 subjects. This discrepancy is not explained. The reanalysis of the data demonstrated that when evaluated for sensitivity to air and cold water stimuli, a significantly greater number of treatment subjects reported excellent improvement at weeks 2, 4, and 8 when compared to the number of placebo subjects reporting excellent improvement. The number of teeth sensitive to these stimuli was also reported to be significantly reduced. No significant differences in sensitivity to the mechanical (scratch) stimulus were observed between the treatment group and the placebo group at any time period. The agency notes that no raw data were submitted with the reanalysis, making it difficult to determine exactly which results were analyzed to establish the significant differences observed between treatments, and the statistical methods used to analyze the data were not well described. Additionally, the agency believes that the mean sensitivity score per subject, rather than using individual teeth, should be the fundamental unit for analysis because the teeth within a patient's mouth cannot be treated as uncorrelated units. Therefore, the agency concludes that neither the published study by Uchida et al. (Ref. 3) nor Wolf's reanalysis of the data (Ref. 15) provides adequate support for the effectiveness of strontium chloride as a tooth desensitizer.

One study by Singh (Ref. 9) was an 8-week, double-blind, controlled clinical study involving the responses of 60 subjects with postperiodontal surgical hypersensitivity to tactile (No. 23 dental probe), and thermal ("gentle burst of compressed air") stimuli. Although the data demonstrated that in all instances the reduction in hypersensitivity observed in subjects using the active dentifrice exceeded that observed in subjects using the placebo dentifrice, only one significant difference was noted. At 8 weeks, a statistically significant superiority of the strontium chloride dentifrice over the placebo dentifrice was reported via a reduction in the number of teeth responding to thermal stimulation. However, because the analyses based on the number of teeth are inadequately described, the validity of the results cannot be determined. All other analyses of measurements resulted in statistical nonsignificance.

Another study by Simring and Collins (Ref. 10) was a 12-week, double-blind, three-way, placebo-controlled investigation of 75 subjects evaluating the effectiveness of a 10-percent strontium chloride dentifrice and a 5-percent potassium nitrate dentifrice in relieving functionally occurring and postperiodontal surgical hypersensitivity. (For a discussion of the effectiveness of potassium nitrate as a tooth desensitizer, see comment 8 above.) The subjects' responses to tactile stimulation (No. 23 dental probe) and thermal stimulation (an unquantified burst of compressed air) were assessed. The study failed to provide evidence of effectiveness. Statistical significance was demonstrated for only 7 out of 120 statistical tests. No significant improvement was observed when the mean sensitivity scores per subject were the units of analysis. Significant improvement could be demonstrated in two tests when individual teeth were used as the fundamental units of analysis. However, as in the Singh study discussed above, the agency does not consider analyses based upon sensitivity scores of individual teeth to be valid. In the other five significant statistical tests, the strontium chloride dentifrice was significantly better than the potassium nitrate dentifrice but not significantly better than the placebo. The agency concludes that these results do not demonstrate or support the effectiveness of strontium chloride as a tooth desensitizer.

In a statistical analysis, Wolf (Ref. 16) combined the data from the study by Singh (Ref. 9) and the study by Simring and Collins (Ref. 10). When the data were combined, no significant differences in tactile total pain scores between the strontium chloride dentifrice and the placebo dentifrice were observed. Significant differences in favor of the strontium chloride dentifrice were noted for the number of teeth reacting to tactile stimuli at 8 weeks ($p < 0.05$). Significant differences in thermal sensitivity total pain scores were observed in favor of the strontium chloride dentifrice at weeks 4 and 8 ($p < 0.05$). Significant differences in the number of teeth responding to thermal stimuli were observed in favor of the

strontium chloride dentifrice at 4 weeks ($p < 0.05$) and at 8 weeks ($p < 0.01$). However, the agency concludes that this pooled analysis is not valid. There is no evidence that these studies were designed with any prior intent to combine the data. Additionally, for some unexplained reason, only the results from 26 of 39 available patients from the Simring study were combined with the results of the Singh study.

A third study by Silverman and Goldman (Ref. 11) was a 4-week, double-blind, three-way, comparative, parallel study of 60 subjects that assessed the effectiveness of a 10-percent strontium chloride dentifrice, a 5-percent potassium nitrate dentifrice, and a placebo dentifrice as tooth desensitizing agents. The subjects' responses to electrical stimulus (pulp stethoscope) and thermal stimulus (1 second blast of cold air, 60 psi at 70 °F) were measured and analyzed. Subjective evaluations were also recorded and analyzed. The 10-percent strontium chloride dentifrice was shown to be significantly better than the placebo at only one time point and by only one method of measurement (i.e., pulp stethoscope stimulus results at week four). Although the results of this study support the desensitizing effectiveness claim for potassium nitrate (see comment 8 above), they do not support the desensitizing effectiveness claim for strontium chloride.

Another study by Silverman (Ref. 12) evaluated the effectiveness of a 10-percent strontium chloride dentifrice in a 12-week, double-blind, placebo-controlled, comparative study of 90 subjects with hypersensitive teeth. Hypersensitivity levels were assessed at 2-week intervals by thermal stimulus (1-second blast of cold air, 60 psi at 70 °F), tactile stimulus (No. 23 dental probe), and subjective response. The strontium chloride dentifrice caused decreases in hypersensitivity, beginning at the 2d week and increasing continuously until the 12th week; however, these decreases in dentinal hypersensitivity were statistically significantly greater than the decreases in dentinal hypersensitivity caused by the placebo ($p \leq .05$) only at the 12-week assessment period for thermal stimuli and subjective response. The agency concludes that this study does not support the effectiveness of 10 percent strontium chloride as a tooth desensitizer.

In the fifth study by Axelrod and Minkoff (Ref. 13), the desensitizing effectiveness of a 10-percent strontium chloride dentifrice and a 5-percent potassium nitrate dentifrice was compared to a placebo dentifrice in a 12-week, double-blind, 3-way comparative study of 45 subjects with dentinal hypersensitivity. Hypersensitivity was assessed thermally (1-second blast of cold air, 60 psi at 70 °F) and evaluated subjectively. Although the results of this study clearly support the effectiveness of potassium nitrate (see comment 8 above), they do not as clearly support the effectiveness of strontium chloride. When measured thermally, the strontium chloride caused a significantly greater reduction in hypersensitivity than the placebo at 4 weeks ($p = .05$), 8 weeks ($p = .01$), and 12 weeks ($p = .01$). However, the subjective response scores for strontium chloride showed no significantly greater decreased in hypersensitivity than for the placebo dentifrice. The agency believes that these data are partially supportive of the effectiveness of strontium chloride as a tooth desensitizer.

Another study by Axelrod and Minkoff (Ref. 14) is partially supportive of the effectiveness of strontium chloride as a tooth desensitizing ingredient. The desensitizing effectiveness of a 10-percent strontium chloride dentifrice was evaluated in a 12-week, double-blind, parallel, comparative study of 61 subjects with dentinal hypersensitivity. Hypersensitivity levels were assessed by thermal (thermally controlled cold air stream) and tactile (Yeaple Probe) stimuli and by subjective evaluation. When hypersensitivity was measured thermally, the strontium chloride dentifrice caused significantly greater reductions in hypersensitivity than the placebo at 8 weeks ($p = .02$) and at 12 weeks ($p = .0001$) but not at 2 or 4 weeks. When measured tactilely, the strontium chloride dentifrice caused significantly greater reductions in hypersensitivity than the placebo at 12 weeks ($p = .02$) but not at any other time period. When assessed subjectively, the strontium chloride dentifrice caused significantly greater reductions in hypersensitivity than the placebo at 4 weeks ($p = .004$), 8 weeks ($p < .001$), and 12 weeks ($p < .001$).

A study by Johnson, Zulgar-Nain, and Koval (Ref. 8) was also submitted in support of the effectiveness of 10 percent strontium chloride. The object of the study was to evaluate an "electro-ionizing" toothbrush for the treatment of dentinal hypersensitivity. Only incidentally was the desensitizing effect of strontium chloride tested. Strontium chloride used with the "electro-ionizing" brush without a battery produced significantly more desensitization at 12 weeks than did the stannous fluoride dentifrice used with the "electro-ionizing" brush without a battery. However, the results of a subjective questionnaire, in which the subjects were asked to note a decrease in hypersensitivity, failed to demonstrate significant improvement when strontium chloride was used. The agency concludes that this study cannot be used to support the effectiveness of 10 percent strontium chloride as a tooth desensitizer.

The agency believes that two of the submitted studies (Refs. 13 and 14) are partially supportive but do not provide sufficient evidence of the effectiveness of 10 percent strontium chloride as a tooth desensitizer. Moreover, based on the overwhelming predominance of nonsignificant improvement in dentinal hypersensitivity observed in the submitted studies, the agency is classifying strontium chloride in Category III as a tooth desensitizer in this amendment.

The agency's detailed comments and evaluation of the data are on file in the Dockets Management Branch (Ref. 19).

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Report," draft of unpublished study, Comment No. C00010, Docket No. 80N-0228, Dockets Management Branch.

(11) Silverman, G., and P. Goldman, "Desensitizing Toothpaste," (DDR study No. 16-78), draft of unpublished study, Comment No. C00010, Docket No. 80N-0228, Dockets Management Branch.

(12) Silverman, G., "Desensitizing Dentifrice Study," draft of unpublished study, Comment No. C00010, Docket No. 80N-0228, Dockets Management Branch.

(13) Axelrod, S., and S. Minkoff, "Desensitizing Toothpaste," (DDR Study No. 15-78), draft of unpublished study, Comment No. C00010, Docket No. 80N-0228, Dockets Management Branch.

(14) Axelrod, S., and S. Minkoff, "Desensitizing Dentifrice Study (10% Strontium Chloride Hexahydrate)," draft of unpublished study, Comment No. C00018, Docket No. 80N-0228, Dockets Management Branch.

(15) Wolf, E.H., "Statistical Summary of a Controlled Clinical Evaluation of a 10% Strontium Chloride Dentifrice in Treatment of Dentin Hypersensitivity Following Periodontal Surgery," draft of unpublished study, Comment No. C00010, Docket No. 80N-0228, Dockets Management Branch.

(16) Wolf, E.H., "Statistical Analysis of Combined Data From Postperiodontal Surgery Subjects in Strontium Chloride Dentifrice Studies Conducted at FDU and UFla," draft of unpublished study, Comment No. C00010, Docket No. 80N-0228, Dockets Management Branch.

(17) Comment No. C00010, Docket No. 80N-0228, Dockets Management Branch.

(18) Comment No. C00018, Docket No. 80N-0228, Dockets Management Branch.

(19) Letter from W.E. Gilbertson, FDA, to S. Most, Block Drug Company, Inc., coded LET13, Docket No. 80N-0228, Dockets Management Branch.

C. Comments on Dosages for Relief of Oral Discomfort Drug Products

10. One comment expressed concern about what it considered the Dental Panel's arbitrary judgment that only concentrations of 85 to 87 percent eugenol are effective as agents for the relief of toothache. The comment contended that lower concentrations of eugenol are also effective for this use, but stated that because of its limited resources, other companies would have to conduct studies to demonstrate the effectiveness of concentrations of eugenol below 85 percent for the relief of toothache.

The Dental Panel's Category I classification of 85 to 87 percent eugenol for the relief of toothache was based on the opinion of experts in endodontics as well as published opinions of other experts that eugenol is a dental analgesic or has a topical anesthetic effect (47 FR 22712 at 22728). The agency, however, does not agree with the Panel's conclusion regarding 85 to 87 percent eugenol and is placing eugenol for the relief of toothache in Category III in this tentative final monograph (see comment 7 above). The Panel also concluded that concentrations of less than 85 percent eugenol may be effective because 85 to 87 percent eugenol is recognized as effective (47 FR 22734). However, because no supportive effectiveness data were available, these lower concentrations of eugenol were placed in Category III. The agency concurs with the Panel's classification of these lower concentrations of eugenol. Other than data on a combination product containing benzocaine (5 percent) and eugenol (less than 85 percent), the comment did not submit any data in support of the effectiveness of concentrations of eugenol at less than 85 percent (see comment 44 below), nor did any other comment submit data that demonstrate the effectiveness of these lower concentrations. Therefore, eugenol as an agent for the relief of toothache at concentrations less than 85 percent remains in Category III.

11. Three comments disagreed with the Dental Panel's Category III classification of phenol in concentrations up to 1.5 percent for the relief of toothache resulting from an open tooth cavity. The comments referred to a statement in the Panel's report in which two acknowledged research experts in endodontics cited phenol's capacity to damage odontoblasts by increasing the permeability of dentinal tubules (47 FR 22712 at 22734). The experts further stated that although phenol may stop pain, its potential to produce pulp damage warrants its elimination from toothache preparations. Citing the minutes of the 5th and 15th Panel meetings in support of their position, the comments stated that the placement of phenol in Category III for safety was based on the Panel's misunderstanding of the presentations made by the two experts (Refs. 1 and 2). The comments contended that the experts were actually referring to the damaging effects of phenol when used at high concentrations and that such effects would not occur with concentrations of 0.5 to 1.5 percent. The comments concluded that phenol concentrations from 0.5 to 1.5 percent will not irritate dental pulp, are safe for use in products for the relief of toothache, and should be placed in Category I for safety.

The agency has reviewed the references cited by the comments and acknowledges that some parts of the discussion concerning the damaging effects of phenol to the pulp, dentin, and dentinal tubules dealt with high concentrations of phenol. However, it cannot be determined from the minutes of the Panel's meetings (Refs. 1 and 2) exactly what concentrations of phenol were being discussed in all cases. The Panel pointed out that there is evidence that some concentrations of phenol can cause irreversible pulp damage (47 FR 22734), and there are no available data demonstrating that phenol in low concentrations is safe for application into an open tooth cavity. In view of the uncertainty regarding the maximum safe concentration of phenol to use as a toothache relief agent for application into an open tooth cavity, the agency agrees with the Panel's conclusion that phenol in concentrations up to 1.5 percent be placed in Category III. The agency invites the submission of data to support the safety and effectiveness of phenol for this use.

References

(1) Ellison, R., presentation to the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products, Summary Minutes of 5th Meeting, October 10 and 11, 1973, in OTC Volume, 08APA2.

(2) Bender, I. B., presentation to the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products, Summary Minutes of 14th Meeting, October 16 and 17, 1974, in OTC Volume 08APA2. (See appendix II of the minutes of the 15th Meeting, December 4 and 5, 1974.)

D. Comments on Labeling for Relief of Oral Discomfort Drug Products

12. 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. A second comment supported the position of the first comment, stating that severely limited wording for indications should be avoided.

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 21 CFR 330.1(c)(2), 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 other OTC drug labeling required by a monograph or other regulation (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under the OTC drug monograph or other regulation where exact language has been established and identified by quotation marks, e.g., 21 CFR 201.63 or 330.1(g).

In this amendment to the tentative final monograph for OTC oral health care drug products, 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 monograph 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.

13. Three comments disagreed with the Dental Panel's recommendation that the name and quantity of each inactive ingredient be listed in the labeling of OTC drug products for the relief of oral discomfort. One comment stated that a list of inactive ingredients in the labeling would be meaningless, confusing, and misleading to most consumers. The comments noted that the act and present regulations do not require that the inactive ingredients of OTC drug products be included on a label and argued that the Panel's recommendation to list these ingredients in descending order of quantity poses additional problems because labels would have to be changed as quantities of inactive ingredients change.

The agency agrees that the Federal Food, Drug, and Cosmetic Act (the act) does not require the identification of all inactive ingredients in the labeling of OTC drug products. Section 502(e) of the act (21 U.S.C. 352(e)) requires that all active ingredients and certain other ingredients, whether included as active or inactive, be disclosed in the labeling. The act also limits the requirement for stating the quantity of ingredients in OTC drug products to those specifically mentioned in section 502(e). Although the act does not require the disclosure of all inactive ingredients in the labeling of OTC drug products, the agency agrees with the Panel that listing of inactive ingredients in OTC drug product labeling would be in the public interest. Consumers with known allergies or intolerances to certain ingredients would then be able to identify substances that they may wish to avoid.

The Nonprescription Drug Manufacturers Association (NDMA) (formerly known as The Proprietary Association), the trade association that represents approximately 85 OTC drug manufacturers who reportedly market between 90 and 95 percent of the volume of all OTC drug products sold in the United States, has established guidelines (Ref. 1) for its member companies to list voluntarily inactive ingredients in the labeling of OTC drug products. Under another voluntary program begun in 1974, the member companies of NDMA have been including the quantities of active ingredients on OTC drug labels. The agency is not at this time proposing to require the listing of inactive ingredients in OTC drug product labeling. However, the agency commends these voluntary efforts and urges all other OTC drug manufacturers to similarly label their products.

Reference

(1) "Voluntary Codes and Guidelines of the OTC Medicines Industry," The Nonprescription Drug Manufacturers Association, Washington, 1991, in OTC Volume 13BTFM.

14. One comment stated that excessive labeling requirements, especially when products are packaged in small containers, would increase consumer cost. The comment requested that only essential information be required on the label.

The agency has reviewed the Dental Panel's recommended labeling and, whenever possible, has revised the labeling so that only information essential for the safe and effective use of the drug is required. The agency believes that the labeling proposed in this amendment is necessary to assure proper and safe use of these OTC drugs by the public. Accordingly, the agency recommends that when any OTC drug product is packaged in a container that is too small to contain all of the required labeling, the product be enclosed in a carton or be accompanied by a package insert that contains the information complying with the monograph. The labeling provisions in 21 CFR Part 201 (e.g., §§ 201.10(i), 201.15, 201.60, 201.61, and 201.62) address various requirements for labeling drugs including drugs packaged in containers too small to accommodate a label with sufficient space to bear all the information required for compliance with various regulations. In those instances where an OTC relief of oral discomfort drug product is packaged in a container that is too small to include all of the required labeling, the product can be enclosed in a carton or be accompanied by a package insert that contains the information complying with the monograph. Manufacturers are also encouraged to print a statement on the product container label, carton, or package insert suggesting that the consumer retain the carton or package insert for complete information about the use of the product when all the required labeling does not appear on the product container label.

The NDMA has recently promulgated guidelines for industry to consider when examining product labels for readability and legibility (Ref. 1). These guidelines are designed to assist manufacturers in making the labels of OTC drug products as legible as possible. The agency commends this voluntary effort and urges all OTC drug manufacturers to examine their product labels for legibility.

Reference

(1) "Points for Consideration in Examining Product Labels for Readability and Legibility," The Nonprescription Drug Manufacturers Association, Washington, April 10, 1990, in OTC Volume 13BTFM, Docket No. 80N-0228, Dockets Management Branch.

15. Two comments concerned the following statements from the Dental Panel's discussion under part C, Labeling for OTC Drug Products for the Relief of Oral Discomfort: "The label should include a clear statement of the usually effective minimum and, where applicable, maximum dose (or concentration if more appropriate) per time interval. If dosage varies with the consumer's age, the directions should be broken down by age groups" (47 FR 22712 and 22719). One comment stated that the wording should be modified to include a gel dosage form and suggested the following wording: "The manufacturer should provide clear instructions as to how the drug should be used including where applicable a minimum and maximum dose, time interval of use and child dosage form if applicable." The other comment

maintained that FDA regulations do not require such labeling, particularly with respect to topical dosage forms. The comment stated that such a requirement would confuse the patient and make it difficult to market a product. The comment requested that the agency clarify that such labeling will not be required.

The agency believes that the Dental Panel's discussion cited above is consistent with agency regulations in 21 CFR 201.5 and § 330.10(a)(4)(v) regarding the labeling of OTC drug products. Directions for use of OTC drug products should be clear, direct, and provide the user with sufficient information to permit safe and effective use of the product. The agency agrees with the Panel that minimum and/or maximum dosages (or concentrations if appropriate), time intervals for doses, and special pediatric labeling, if necessary, are important for proper usage by the consumer. The agency believes that requiring such labeling on OTC drug products for the relief of oral discomfort is neither excessively restrictive nor apt to be so confusing to the consumer that marketing of a product would be precluded or hindered. In addition, the agency points out that the Panel's statement (47 FR 22719) was intended as a general, not a specific, recommendation, and the wording is comprehensive enough to encompass all possible dosage forms including gels. Therefore, the agency is not amending the Panel's report as requested and, in this amendment to the tentative final monograph, is proposing directions for use consistent with the Panel's discussion and existing agency regulations.

16. Four comments objected to the Dental Panel's definition of an agent for the relief of toothache as "an ingredient used for the temporary relief of pain arising as a result of an open tooth cavity." One comment believed that the indication for agents for the relief of toothache should reflect the use of these products for pain "due to" or "associated with" toothache, but should not be limited to instances in which the pain is "throbbing" and "persistent." Two comments stated that pain described as a toothache may be due, among other causes, to cracked or defective fillings, foreign or external objects caught between the teeth or between the teeth and gums, excessive plaque or calculus (calcified tooth deposits), cracks in the dental enamel, or trauma to the jaws or gums. Two of the comments thought the definition was too restrictive and ignored mucosal (gingival) pain, which is generally considered by the lay public to be a "toothache." One comment proposed the following definition: "An ingredient used for the temporary relief of pain due to an open tooth cavity or pain arising from an aching tooth." Another comment suggested that the definition should be broadened as follows: "An oral discomfort agent for the temporary relief of: 'Toothache due to open cavity' or 'Pain arising from an aching tooth'." In support of extending toothache claims to pain not associated with an open tooth cavity, this comment and another comment contended that a survey of 966 people (Ref. 1) demonstrated that consumers do not limit their definition of toothache pain to "pain arising from an open tooth cavity," but use the same word "toothache" generically to describe any pain in or about the mouth, jaw, and gums, as well as the teeth. One comment added that topical analgesics, such as benzocaine and phenol, are safe and effective for the temporary relief of "toothache," even if the pain is not due to an "open tooth cavity" and the dental pulp is not irreversibly damaged. Another comment objected to the Panel's not including a claim for pain associated with toothache among the claims for oral mucosal analgesics. The comment requested that a claim for the temporary relief of pain, commonly referred to as "toothache pain" as differentiated from pain due to an open tooth cavity, be placed in Category I for oral mucosal analgesic ingredients.

The Dental Panel began its general discussion of agents for the relief of toothache by describing the significance of an open cavity in a tooth (47 FR 22712 at 22725). A normal, healthy tooth contains a layer of protective enamel directly above a layer of dentin. The dentin encloses the soft tissues of the pulp, which are very susceptible to any irritation occurring in a cavity. Irritation causes inflammation leading to either a reversible or an irreversible stage of pulp disease. A tooth in the irreversible stage is characterized by a persistent, throbbing pain. If the pain is intermittent, rather than persistent, the pulp damage may be reversible.

The Dental Panel limited the definition of an agent for the relief of toothache to ingredients for the temporary relief of throbbing, persistent toothache resulting from a cavity. The Panel based its definition on the assumption that, in general, agents that have historically been used for the relief of toothache are irritating to viable dental pulp and should only be used on a tooth with irreversible pulp damage. Such agents should not be used on a tooth with reversible pulp damage, i.e., a tooth with intermittent pain, because the agent could exacerbate the condition and cause the tooth to die. (Although the Panel placed eugenol in Category I as an ingredient for the relief of toothache, the agency is placing the ingredient in Category III for such use and, consequently, there are no Category I ingredients for the relief of toothache in this document. See comment 7 above.)

The agency has received other comments which have requested a Category I indication for benzocaine as an agent for the relief of toothache (see comment 5 above). The Dental Panel placed benzocaine in Category III as an agent for the relief of toothache. The Panel considered benzocaine safe, but the available data were insufficient to show that benzocaine was effective in relieving toothache pain after application into a tooth cavity (47 FR 22712 at 22730). The agency has reviewed both the data submitted to the Panel and additional data submitted in response to the Panel's report and finds that the data do not support the reclassification of benzocaine from Category III to Category I as an agent for the relief of toothache. Although benzocaine is far less caustic than eugenol, it is not effective as an anodyne when instilled into a cavity in a tooth with irreversible pulp damage. Benzocaine is more effective in relieving pain when it is applied to the oral mucosa.

The agency has reviewed the results of the consumer survey (Ref. 1) which two comments contended showed that toothache pain should not be restricted to pain associated with an open tooth cavity. The agency finds that this survey shows that the American public uses the word "toothache" in a generic sense to indicate pain in or about the mouth, jaw, and gums, as well as the teeth, but that it does not support extending a toothache claim to pain that is not associated with an open tooth cavity. Of the 82 percent of the respondents who reported ever having had a toothache, 65 percent had their toothache caused by a tooth problem, i.e., pain caused by a cavity (41 percent), tooth decay (16 percent), or a cracked filling (8 percent). When asked the location of the pain experienced during their last toothache, only 26 percent reported the pain as located in the tooth itself. The survey did not adequately address consumers' ability to determine whether the pain is due to a toothache. In fact, the survey indicates that there is a great difference between consumers' perception of the location of the "toothache" pain and the actual cause of the pain. Because consumers who self-diagnose pain in or

about the mouth are often unable to determine the exact location of the cause of the pain, it is important that OTC drug products contain the proper indications to assist them in selecting the correct product. Therefore, the agency believes that it is important that the definition and indications for these products be restricted to pain associated with an open tooth cavity, a condition readily recognizable to consumers, to ensure proper use of these products.

With respect to the other comments' contention that oral mucosal analgesics are effective in relieving "toothache," oral mucosal analgesics are indicated for such conditions as the relief of pain due to minor irritation or injury of soft tissue of the mouth but have not been shown to be effective in relieving "toothache" due to a cavity. In the survey submitted by the comment, the majority of respondents who had "pain associated with a toothache" actually had a problem with a tooth, e.g., a cavity or decay. It would be inappropriate for an oral mucosal analgesic to have an indication for the relief of "pain associated with a toothache" when the pain is caused by a problem with the tooth itself and not the surrounding soft tissue. Therefore, the agency agrees with the Dental Panel that agents for the relief of toothache should be restricted to ingredients placed in a tooth cavity to relieve throbbing, persistent pain resulting from an open cavity in the tooth. Moreover, oral mucosal analgesics that relieve pain arising from an injury to adjacent soft tissue should not be indicated for the relief of pain due to a problem inherent to a tooth. Accordingly, the agency does not accept the comments' request to change the definition of an agent for the relief of toothache or to place in Category I for oral mucosal analgesic ingredients a claim for the temporary relief of pain, commonly referred to as "toothache pain" as differentiated from pain due to an open tooth cavity.

Reference

(1) Comment No. C00007, Docket No. 80N-0228, Dockets Management Branch.

17. One comment objected to the Dental Panel's recommendation that the labeling of OTC drug products for the relief of oral discomfort indicate the principal intended action of each active ingredient (47 FR 22712 at 22718). The comment indicated that if a statement of general pharmacological activity is present, a statement of principal intended action of active ingredients would often be simply redundant and that the use of pharmacological terms describing principal intended actions might be confusing to some consumers.

The agency agrees in part and disagrees in part with the comment. The comment is correct in stating that if a statement of general pharmacological activity is present, then a statement of principal intended action of active ingredients would likely be redundant. The agency has reviewed the Panel's recommendation and believes that the Panel was simply recommending that each product for the relief of oral discomfort bear a statement of identity in accord with 21 CFR 201.61, which the Panel cited at 47 FR 22718. This recommendation for OTC drug products for the relief of oral discomfort is consistent with the labeling for all OTC drug products in that 21 CFR 201.61 requires the statement of identity to be in terms of the established name of the drug, if any, followed by an accurate statement of the general pharmacological category(ies) of the drug or the principal intended action(s) of the drug. The regulation further requires that such statements shall employ terms descriptive of general pharmacological category(ies) or principal intended action(s), and cites as examples the terms "antacid," "analgesic," "decongestant," "antihistaminic," etc. The agency is designating and proposing one or more terms such as these as the "statement of identity" for the various product classes included in this tentative final monograph after considering the Panel's recommendations and other suggested terms submitted in the comments. (See comment 18 below.)

18. Two comments objected to the Dental Panel's recommended "Statement of identity" for tooth desensitizers in § 354.65(a). The comments believed the recommended term "tooth desensitizer" is overly restrictive, not adequately descriptive, and potentially confusing to consumers because it could conceivably mislead them by incorrectly suggesting a new use for these products, such as toothache relief or oral analgesia. The comments suggested that other terms such as "toothpaste for sensitive teeth" or "desensitizing toothpaste" should be permitted. One of the comments added that the term "desensitizing toothpaste" had been used for over 20 years for one of its products, has had wide acceptance, and is readily understood. A third comment objected to the Panel's restrictiveness in proposing to allow only one statement of identity in the labeling of tooth desensitizer drug products. The comment argued that FDA should allow manufacturers the alternatives set forth in existing agency regulations regarding the statement of identity for OTC drug products (21 CFR 201.61), which state that the label shall include the established name of the drug, if any, followed by an accurate statement of the general pharmacological category(ies) of the drug or the principal intended action(s) of the drug. If the drug is a combination that has no established name, the requirement may be satisfied by placing a prominent and conspicuous statement of the general pharmacological action(s) of the combination or its principal intended action(s), in terms that are meaningful to laymen.

The agency agrees with the comments that the term "tooth desensitizer" may be misleading to consumers because it may suggest to them that the product can be used for purposes other than its intended use, e.g., as a toothache remedy or an oral analgesic. The agency has reviewed the labeling of tooth desensitizer drug products and agrees that other descriptive terms could be used. The agency believes that the most descriptive term would be that the product is a toothpaste (or dental gel) for sensitive or hypersensitive teeth. The agency believes that the term "desensitizing toothpaste" is similar to "tooth desensitizer" in that it may suggest to consumers that the product can be used for conditions other than the treatment of sensitive teeth, e.g., the relief of toothache. As the Dental Panel explained in its general discussion of agents used to treat "hypersensitive" (ultrasensitive) teeth (47 FR 22712 at 22749), hypersensitivity in teeth develops when the dentin is exposed to the environment of the oral cavity. The dentin, which contains the sensory mechanism of the tooth, can become ultrasensitive to various stimuli such as temperature change, mechanical stimuli, and certain chemicals. Because the development of hypersensitive teeth is complex and may occur for many different reasons, e.g., erosion or abrasion of calcified structures, the diagnosis of this condition should be made by a dentist.

It is important that products containing tooth desensitizing ingredients be clearly labeled for this purpose and not mistakenly used to treat other conditions involving the teeth or gums. Thus, the agency is proposing in this amendment that the statement of identity recommended by the Panel in § 354.65(a) (which appears in § 356.62(a) in this proposal) be revised as follows: The labeling of the product contains the established name of the drug, if any, and identifies the product as a (insert dosage

form, e.g., "toothpaste" or "dental gel") "for" (select one of the following: "sensitive" or "hypersensitive") "teeth."

19. Referring to agents for the relief of toothache, one comment disagreed with the Dental Panel's Category II classification of labeling claims such as "stops pain," "soothes sore gums," and "alleviates pain" (47 FR 22712 at 22730) and any claims that such a product "provides soothing relief." the comment asserted that it failed to understand why such terms are considered too vague and maintained that the terms are useful to the consumer and should be allowed, as long as the product's label contains accepted indications for use as recommended by the Panel in § 354.50(b).

The Panel stated in its report that indications for the use of an "agent for the relief of toothache should be simply and clearly stated and should provide the user with a reasonable expectation of results to be anticipated from use of the product" (47 FR 22719). The agency believes that the term "stops" on the label of agents for the relief of toothache could be misleading and subject to misinterpretation by consumers. The claim "stops pain" implies that pain will not resume and does not provide the consumer with a reasonable expectation of the duration of relief provided by an OTC drug product. Therefore, the agency agrees with the Panel's Category II classification of the labeling claim "stops pain."

The agency believes that the term "soothing" is a product attribute describing certain physical and chemical qualities of an OTC drug product. However, such product attributes are not indications for use, but merely factual statements related to product performance. The agency has no objection to the use of terms describing certain physical and chemical qualities of a drug, as long as these terms do not imply that any therapeutic effect might occur, are true and not misleading, and are distinctly separated from labeling indications. Terms describing a product's characteristics (e.g., color, odor, flavor, and feel) may appear in the labeling for the consumer's information. The agency concludes that it is not necessary to include terms such as these in this amendment.

The agency believes that "alleviates" is an acceptable term, and manufacturers should have the option to use this term in the indications for toothache relief drug products. The agency is therefore proposing to revise the Panel's recommended indication for relief of toothache drug products as follows: "Temporarily" (select one of the following: "alleviates" or "relieves") "throbbing, persistent toothache due to a cavity until a dentist can be seen."

The agency is not proposing any Category I agents for the relief of toothache in this amendment. Consequently, the agency is not including labeling for agents for the relief of toothache in this document. In the even that an ingredient for the relief of toothache reaches monograph status (Category I), the agency will include labeling, as discussed above, in the final monograph.

20. Two comments disagreed with the Dental Panel's placement of certain claims in Category II, specifically, "For temporary relief of cavity toothache" (47 FR 22712 at 22730 and 22742), "* * * [R]elief from toothache due to cavities," "Eases pain due to cavities * * *" (47 FR 22730), and "Temporary relief for toothache due to cavities" (47 FR 22742). Noting that the Panel placed these claims in Category II because the claims could be considered "misleading and unsupported by scientific data" (47 FR 22730), one comment maintained that some of these claims are simply alternative ways of stating claims that the Panel placed in Category I or are statements that merely describe the product's action. The second comment argued that the claims "For temporary relief of cavity toothache" and "Temporary relief for toothache due to cavities" are within the acceptable parameters of the Panel's recommended indication for agents for the relief of toothache in § 354.50(b) (47 FR 22758). The comment added that, in light of the agency's announced intention to ease the so-called OTC "Exclusivity Rule," published in the **Federal Register** of July 2, 1982 (47 FR 29002), these claims should be classified as Category I.

Two of the above labeling claims, "* * * [R]elief from toothache due to cavities" and "Eases pain due to cavities * * *," when evaluated by the Panel, included the term "fast." For a discussion of terms that refer to the onset of action of the drug, such as "fast." (See comment 25 below.)

The Panel recommended the following indication for agents for the relief of toothache: "For the temporary relief of throbbing, persistent toothache due to a cavity until a dentist can be seen." The agency agrees with the Panel regarding the importance of emphasizing that eugenol, if it should become a Category I ingredient for the relief of toothache, should only be used when "throbbing, persistent pain" exists. (See comment 21 below.) In its general discussion of agents for the relief of toothache and its discussion of eugenol (47 FR 22712 at 22725 to 22727), the Panel stated that irritating substances (e.g., eugenol) should only be applied to a nonviable tooth with irreversible damage (characterized by throbbing, persistent pain) because the application of an irritating substance is likely to further injure a viable tooth that has reversible damage (characterized by intermittent pain).

The agency considers the claims proposed by the comments as not providing consumers sufficient information for the safe and effective use of these products because the claims do not include the definitive terms "throbbing" and "persistent." For this reason, and irrespective of the easing of the exclusivity policy (see comment 12 above), the agency concludes that these claims are not suitable alternative ways of stating the claim proposed by the Panel for agents for the relief of toothache, nor are they statements describing the product's action. Although the claims proposed by the comment might be appropriate for nonirritating agents for the relief of toothache, no such agents are currently classified in Category I. (See comment 21 below.) The agency will further consider such claims should a nonirritating agent for the relief of toothache attain Category I status. At this time, however, because there are no Category I ingredients for the relief of toothache, the agency is not including any "relief of toothache" claims in this amendment. In the event that an ingredient for the relief of toothache reaches monograph status (Category I), the agency will include the Panel's recommended indication in the final monograph.

21. Two comments requested that the indication recommended by the Dental Panel in § 354.50(b), "for the temporary relief of throbbing, persistent toothache due to a cavity * * *," be limited to 85 to 87 percent eugenol and not extended to apply to any ingredient that may be classified in Category I in the future. One of the comments stated that limiting the use of toothache remedies to teeth with persistent, throbbing pain is unnecessary for nonirritating ingredients such as benzocaine. The comment maintained that patients cannot readily assess their own level of pain and that they will desire relief regardless of the level of pain. Stating that there are instances when a consumer desires relief from a toothache that is causing less than persistent, throbbing pain and contending that the labeling proposed by the Panel would discourage the use of these products in such instances, the comment maintained that there were no facts to support such a stringent

requirement for a drug as safe as benzocaine.

The agency recognizes that all ingredients that may become Category I agents for the relief of toothache may not be irritating and harmful to a viable dental pulp. The Panel described the types of toothache pain that differentiate between a viable dental pulp and a nonviable dental pulp. It stated that intermittent toothache pain indicates that the dental pulp is still viable and that persistent, throbbing pain indicates that the dental pulp is no longer viable (47 FR 22712 at 22728). The Panel recommended an indication for throbbing, persistent toothache for eugenol, the only agent for the relief of toothache that it put in Category I ingredient, because it is known to be irritating and potentially harmful to viable dental pulp (47 FR 22727). The agency, however, disagrees with the Panel's Category I classification of eugenol used for the relief of toothache. Therefore, in this amendment, the agency is placing eugenol in Category III and is not including any labeling for ingredients for the relief of toothache (see comment 7 above). If eugenol is upgraded to monograph status (Category I), the agency will include the Panel's recommended indication for eugenol in the final monograph.

The agency recognizes that the Panel recommended the same indication, i.e., the persistent, throbbing pain, for all Category III active ingredients for the relief of toothache. Other ingredients may be safe for use in a viable tooth when the toothache pain is not persistent and throbbing. Therefore, the agency agrees with the comment that the indication "for the temporary relief of throbbing, persistent toothache" would not be necessary for such ingredients. If any Category III ingredient for the relief of toothache is upgraded to Category I, and if sufficient data are submitted to the agency demonstrating that the ingredient does not further damage irritated, but viable, dental pulp, the agency will consider an appropriate indication that provides for the safe use of the ingredient.

22. One comment believed that terms for oral mucosal analgesics such as "helps comfortable adjustment" and "unaccustomed use," which the Dental Panel placed in Category II, should be allowed as Category I if used in conjunction with a Category I claim such as "for the temporary relief of pain due to minor irritation of soft tissue due to dentures or orthodontic appliances."

The Panel placed terms such as "helps comfortable adjustment" and "unaccustomed use" in Category II on the basis that they are vague and not definitive of the condition for which relief is sought (47 FR 22712 at 22742). The Panel listed four indications that it felt adequately describe the conditions for which an oral mucosal analgesic should be used (47 FR 22740). All of these indications concern the "temporary relief of pain" due to various conditions, such as minor irritation caused by dentures or injury of soft tissue of the mouth. The Panel did not believe that these Category I indications would be improved by the addition of terms such as "helps comfortable adjustment" or "unaccustomed use," which are not directly related to conditions causing pain. The agency concurs with the Panel and thus rejects the comment's contention that these Category II terms should be allowed in an indication if used in conjunction with a Category I claim.

23. One comment objected to the Dental Panel's recommended requirement in § 354.55(b)(1)(iv) that the indication for use of an oral mucosal analgesic for the relief of pain due to canker sores carry the statement "when the condition has been previously diagnosed by a dentist." The comment stated that canker sores are mucosal lesions commonly diagnosed by consumers, are generally self-limiting, and seldom lead to complications. The comment added that requiring an individual to seek professional advice prior to treatment of a canker sore with proven safe and effective local anesthetics is not in the best interest of the consumer. The comment requested that § 354.55(b)(1)(iv) be revised to read as follows: "For the temporary relief of pain due to canker sores."

In the tentative final monograph for OTC oral mucosal injury drug products (48 FR 33984 at 33989), the agency discussed the self-treatment of canker sores with OTC drug products. The agency stated that, because the term "canker sores" has been used in the labeling of marketed OTC drug products for many years, consumers have a general understanding of the term and do not require a professional diagnosis by a dentist before using an OTC drug product to cleanse a canker sore. Additionally, in the first segment of the tentative final monograph for OTC oral health care drug products (53 FR 2436 at 2458), the agency proposed the following indication for oral health care anesthetic/analgesics in § 356.55(b)(2): "For the temporary relief of pain associated with canker sores." Because oral mucosal analgesics are being combined with oral health care anesthetic/analgesics in this amendment (See part II. paragraph B.5. below), the indication proposed in § 356.55(b)(2) will apply to oral mucosal analgesic ingredients. The indication appears in § 356.52(b)(2) in this amendment. The agency believes that this proposed indication responds to the concerns expressed by the comment.

24. Referring to oral mucosal analgesic drug products, one comment disagreed with the Dental Panel's Category II classification of the labeling claims "For * * * temporary relief of pain and soreness due to minor irritation of teeth and gums," "For * * * effective relief of sore gums," and "For * * * temporary relief of minor mouth or gum soreness" (47 FR 22712 at 22742). The comment maintained that these claims are simply alternative ways of stating claims that the Panel placed in Category I or are statements that describe the product's action. The comment recommended that these Category II claims be moved to Category I.

The above labeling claims, when evaluated by the Panel, included the terms "quick," "rapid," and "fast." For a discussion of terms such as these that refer to the onset of action of the drug, see comment 25 below. The Panel classified the first two claims mentioned by the comment in Category II because, based on the available evidence, it concluded that the claims are misleading and unsupported by scientific data (47 FR 22742). The third claim was also classified in Category II because the Panel judged this claim to be "too vague" and recommended that "it must be more specific" (47 FR 22742).

The agency concurs with the Panel and further considers the comment's version of the first cited claims, "For * * * temporary relief of pain and soreness due to minor irritation of teeth * * *," to be unacceptable because the Category I indications for oral mucosal analgesics do not include relief of pain and soreness due to irritation of teeth. Oral mucosal analgesics are intended for use on soft tissues, and the agency concludes that a claim related to irritation of teeth is not acceptable for products containing ingredients in this class.

In the tentative final monograph for OTC oral mucosal injury drug products, published in the **Federal Register** of July 26, 1983 (48 FR 33984), the agency proposed to replace the phrase "oral soft tissues" with the phrase "mouth and gums." The agency believes that the phrase "oral soft tissues" lacks precise meaning for most consumers and that the phrase "mouth and gums" will be more readily understood by consumers. Therefore, in this amendment, the agency is proposing to revise the indications recommended by the Dental

Panel in § 354.55(b)(1)(i) and (iii) and § 354.55(b)(3) by using the phrase "mouth and gums" instead of "soft tissues," "soft tissue of the mouth," or oral tissues." Because of the similarities between oral mucosal analgesics and oral health care anesthetic/analgesic ingredients, the agency is proposing in this amendment to combine the two categories. (See part II. paragraph B.5. below.) Therefore, the agency is also proposing to combine these revised indications for oral mucosal analgesics and the indications for oral health care anesthetic/analgesics proposed by the agency in § 356.55(b) of the first segment of the tentative final monograph for OTC oral health care drug products and to include these revised and combined indications in § 356.52(b) of the amended tentative final monograph.

25. One comment expressed concern that all claims which state that a product provides "fast," "quick," or "rapid" relief have been placed in Category II. The comment stated that such claims should be Category I for any product containing benzocaine because, as the Dental Panel noted, benzocaine "has an almost immediate onset of action" (47 FR 22712 at 22738). Claiming that the effect is well known and is evidenced in the scientific literature, the comment expressed its belief that a claim that a product containing benzocaine provides "fast," "quick," or "rapid" temporary relief of toothache pain is founded in scientific fact and should be allowed. A second comment contended that terms such as "fast" and "quick" are not inherently misleading and should therefore be permitted in the labeling of products that can demonstrate such onset of action through scientific data.

As with all OTC drug products, relief of oral discomfort drug products containing benzocaine are expected to achieve their intended results within a reasonable period of time. However, the specific period of time within which relief of oral discomfort drug products achieve these results is not related in a significant way to the safe and effective use of the products. Accordingly, terms such as "fast," "quick," or "rapid" would not signal any property that is important to the safe and effective use of these products and these terms are outside the scope of the OTC drug review and will not be addressed in this amendment. For other classes of products in the OTC drug review, however, statements relating to time of action may properly fall within the list of terms covered by the monograph.

Excluding such terms from the monograph does not imply that they cannot appear in the labeling of a product provided they meet the provisions in section 502 of the act (21 U.S.C. 352) relating to labeling that is false or misleading. Such terms will be evaluated by the agency in conjunction with normal enforcement activities relating to that section of the act. Moreover, any term that is outside the scope of the monograph, even though it is truthful and not misleading, may not appear in the boxed area of the labeling entitled "FDA Approved Uses" or "FDA Approved Information" and may not detract from such required information. (See comment 12 above.)

26. Three comments objected to the Dental Panel's Category II classification of the claim "Builds increasing protection against painful sensitivity to cold, heat, sweet, sour, or contact," and claims that imply a superiority in onset of action, such as "quicker," "more quickly," and "faster" for tooth desensitizing ingredients (47 FR 22712 at 22751). The comments maintained that these claims should be classified in Category I if they are supported by adequate scientific documentation.

One comment stated that because improving sensitivity scores with time is commonplace in the various chemical investigations of tooth desensitizing ingredients, the claim "Builds increasing protection * * *." is valid. The comment maintained that the Panel's reasoning that "This Claim implies a slow mechanism of action." (47 FR 22751) is irrelevant to the claim's validity. However, another comment stated that daily use of a tooth desensitizing product for a period of weeks does show a decrease in hypersensitivity and that, accordingly, there is indeed a slow mechanism of action seen in the therapeutic responses to tooth desensitizing ingredients during a study. Therefore, the comment stated that the claim "Builds increasing protection * * *." is valid and important information.

Regarding claims that imply a superiority in onset of action, such as "quicker," "more quickly," and "faster," one comment maintained that if data demonstrate that one agent relieves sensitivity in 1 week whereas another agent relieves sensitivity in 3 weeks, the first agent is obviously therapeutically "faster" than the second. The comment contended that this is important consumer protection information that should be encouraged when supported by sound scientific data.

The OTC drug review establishes conditions under which OTC drugs are generally recognized as safe and effective and not misbranded. Two principal conditions examined during the review are allowable ingredients and allowable labeling. FDA has determined that it is not practical—in terms of time, resources, and other considerations—to set standards for all labeling found in drug products. Accordingly, OTC drug monographs regulate only labeling related in a significant way to the safe and effective use of covered products by lay persons. OTC drug monographs establish allowable labeling for the following items: Product statement of identity; names of active ingredients; indications for use; directions for use; warnings against unsafe use, side effects, and adverse reactions; and claims concerning mechanism of drug action.

The agency believes that the claim "Builds increasing protection against painful sensitivity to cold, heat, sweet, sour, or contact" is related to the therapeutic effectiveness of the drug product and is derived from data concerning the mechanism of drug action. Data submitted to the agency in support of the effectiveness of potassium nitrate as a tooth desensitizer (Refs. 1 and 2) indicate that the desensitizing effectiveness of potassium nitrate increases with time, up to 12 weeks. For example, in a 12-week study by Axelrod and Minkoff (Ref. 3), subjects using a dentifrice containing potassium nitrate showed the following subjective decreases in sensitivity: 15 percent at 2 weeks, 42 percent at 4 weeks, 50 percent at 8 weeks, and 75 percent at 12 weeks. The subjects showed comparable decreases in sensitivity when their tactile responses and cold air responses were measured. (See comment 8 above.)

The agency believes that these results indicate that potassium nitrate's effectiveness as a tooth desensitizer is cumulative and that such information should be available to consumers because it might take 2 or 3 weeks before significant therapeutic relief is obtained from the use of a potassium nitrate dentifrice. Therefore, the agency agrees with the comments that the claim "Builds increasing protection * * *." is appropriate for tooth desensitizers such as potassium nitrate, which at this time is the only Category I tooth desensitizer. Therefore, in this amendment, the agency is proposing the following additional indication in § 356.62(b)(2): "Builds increasing protection against painful sensitivity of the teeth to cold, heat, acids, sweets, or contact."

However, the agency believes that unspecified periods of time, such as

"quicker," "more quickly," or "faster," implying prompt relief are not related in a significant way to the safe and effective use of tooth desensitizers and thus are outside the scope of the OTC drug review. As with all OTC drug products, tooth desensitizers are expected to achieve their intended results within a reasonable period of time. As discussed above, it might take 2 or 3 weeks before significant therapeutic relief is obtained from the use of potassium nitrate dentifrice. Therefore, terms such as "quicker," "more quickly," or "faster" do not seem to be appropriate for OTC tooth desensitizers. For other classes of products in the OTC drug review, such as bronchodilators, statements relating to onset of action may properly fall within the list of terms covered by the monograph.

The agency emphasizes that even though terms such as "quicker," "more quickly," or "faster" are outside the scope of the OTC drug review for this class of products, they are subject to the provisions in section 502 of the act (21 U.S.C. 352) relating to labeling that is false or misleading. Such terms will be evaluated by the agency in conjunction with normal enforcement activities relating to that section of the act.

Moreover, any term that is outside the scope of the review, even though it is truthful and not misleading, may not appear in any portion of the labeling required by the monograph and may not detract from such required information. However, statements and terms outside the scope of the monograph may be included elsewhere in the labeling, provided they are not false or misleading.

References

(1) Comment No. C00011, Docket No. 80N-0228, Dockets Management Branch.

(2) Comment No. C00012, Docket No. 80N-0228, Dockets Management Branch.

(3) Axelrod, S., and S. Minkoff, "Desensitizing Dentifrice Study, 1981," draft of unpublished study, Comment No. C00011, Docket No. 80N-0228, Dockets Management Branch.

27. One comment indicated that excessive warning statements should be avoided. It claimed that to preface consumer advice that does not concern life-threatening, or even dangerous, situations with the word "warning" simply encourages the reader to ignore labeling which should be read.

The agency agrees that excessive warning statements should be avoided. For example, the Dental Panel's recommended warning "Children under 12 years of age should be supervised in the use of this product" is not included in the warnings section of this proposal because the statement appears in the directions for use. However, concerning the use of the term "warning," section 502(f)(2) of the act (21 U.S.C. 352(f)(2)) provides, in part, that any marketed drug must bear in labeling "* * * such adequate warnings * * * as are necessary for the protection of users * * *."Furthermore, § 330.10(a)(4)(v) of the OTC drug regulations (21 CFR 330.10(a)(4)(v)) requires that the labeling of OTC drug products include "* * * warnings against unsafe use, side effects, and adverse reactions * * *." Thus, the agency concludes that it is insufficient to limit statements in the "Warnings" section of the labeling to life-threatening or highly dangerous situations only. OTC labeling must also warn against unsafe use of the product and alert consumers of possible side effects even if not likely to be life-threatening or highly dangerous. The agency encourages consumers to read fully all warnings information because the statements included in this section of the labeling are considered important to the proper safe use of the product.

28. A number of comments objected to the warning "Do not swallow" that was recommended by the Dental Panel for all drugs for the relief of oral discomfort. Several comments stated that oral mucosal analgesics and agents for the relief of toothache are placed on the gums or in a tooth and therefore it would be difficult for the patient not to swallow some of the drug. Moreover, the comments argued that because the drugs have been found safe for use in the mouth, such a requirement is illogical and unnecessary. The comments also stated that this warning could unnecessarily alarm consumers and cause them to believe that swallowing even small quantities of the product would result in substantial harm. One comment believed that consumers might misinterpret the warning to mean that one should totally refrain from the act of swallowing rather than to refrain from swallowing excessive amounts of the product. Another comment stated that the warning should not be required for tooth desensitizers because such products are used by adults, who do not appreciably ingest identifrices. The comment added that this warning should be reserved for conditions where there is a reasonable basis for concern based on the safety record of the ingredient or on the use pattern.

The agency agrees with the comments that the warning "Do not swallow" is not needed for drug products included in this rulemaking for the relief of oral discomfort. The agency believes that products such as oral mucosal analgesics, agents for the relief of toothache, and oral mucosal protectants that are directly applied in small amounts to small areas of the oral mucous membranes or to the teeth (e.g. as a liquid or gel) do not require such a warning. These products are not intended to be used in large amounts in the mouth, and the small amount of drug that an individual would undoubtedly swallow would cause no harm. Therefore, the agency will not include the warning "Do not swallow," which was recommended by the Panel for agents for the relief of toothache, oral mucosal analgesics, and oral mucosal protectants in §§ 354.50(c)(1)(iv), 354.55(c)(1)(iii), and 354.60(c)(3), respectively. However, for oral mucosal analgesics formulated as a mouthwash (oral rinse), the agency believes that the directions for use of the product should state that the product should be spit out after rinsing. The agency is including the wording "* * * and then spit out" in the directions for mouthwashes (oral rinses) in § 356.52(d)(1)(i), (d)(2)(i), (d)(4)(i), (d)(5)(i), (d)(6)(i), (d)(7)(i)(A) and (B), and (d)(8)(i) of this proposal.

Both tooth desensitizers and fluoride dentifrices are used in the same manner, i.e., brushed on the teeth with a toothbrush and then spit out. The Panel did not recommend and the agency did not propose a warning concerning the avoidance of swallowing for fluoride dentifrices because these products hav a long history of safe use (see the advance notice of proposed rulemaking for OTC anticaries drug products published in the **Federal Register** of March 28, 1980 (45 FR 20666 at 20682) and the tentative final monograph for OTC anticaries drug products published in the **Federal Register** of September 30, 1985 (50 FR 39854 at 39864)). Accordingly, the agency believes that such a warning is not warranted for tooth desensitizer drug products. In addition, as stated by the comment, tooth desensitizers are recommended for adult use and not for children under 12 years of age, thus there is little likelihood that the intended population would ingest the product. The Dental Panel stated that, even in children aged 3 to 6 years, the large majority swallow less than 0.5 gram of toothpaste per brushing (47 FR 22712 at 22751). Adults could be expected to swallow even less. For these reasons, the agency is not including in this proposal the warning regarding swallowing that was recommended by the Panel for tooth desensitizer drug products in § 354.65(c)(2).

29. One comment objected to the Dental Panel's statement in 47 FR 2271

at 22726 that "most toothache remedies are very caustic preparations which will burn the oral mucosa" insofar as it purports to apply to benzocaine. The comment noted that benzocaine, as stated by the Panel, "is one of the more widely used and safest topical anesthetics found in OTC preparations" (47 FR 22737). The comment added that the Panel found the irritancy and sensitivity incidence of benzocaine were at levels of other commonly used drugs (47 FR 22738), and that the Panel did not believe a warning as to that effect was required for the ingredient. The comment requested that, should benzocaine be placed in Category I, the "irritation" warning recommended by the Panel in § 354.50(c)(1)(iii) should not apply to products containing benzocaine.

The Dental Panel's statement referred to by the comment was part of a general discussion on toothache remedies. It is not clear in the discussion to what preparations the Panel was referring. It is possible that the Panel was referring to eugenol, which it stated is known to be very caustic (47 FR 22727). In addition, the Penal described this statement as pertaining to "most," not "all," toothache remedies. The agency believes that the Panel did not intend for the statement to apply to benzocaine because the Panel stated elsewhere in its report that the incidence of benzocaine irritancy equals that of other commonly used drugs and is less than that of the more frequently used sensitizer (47 FR 22738).

The "irritation" warning in § 354.50(c)(1)(iii) referred to by the comment states, "If irritation persists, inflammation develops, or if fever and infection develop, discontinue use and see your dentist or physician promptly." This statement was proposed as a general warning required for all Category I ingredients in all classes of drug products for the relief of oral discomfort (i.e., agents for the relief of toothache, oral mucosal analgesics, oral mucosal protectants, and tooth desensitizers). The warning statement does not refer to any specific ingredient, but rather refers to the condition that is being treated. If the condition does not improve or if it worsens, the consumer is instructed to seek professional treatment. Therefore, the agency does not accept the comment's claim that the warning statement is not applicable to benzocaine.

As discussed in comment 5 above, benzocaine remains in Category III as an agent for the relief of toothache in this amendment. However, even if sufficient effectiveness data are submitted to reclassify benzocaine to Category I, the agency will still require the general warning statement recommended by the Panel in § 354.50(c)(1)(iii) of its report or a similar warning.

30. Three comments objected to many of the warnings proposed by the Dental Panel for tooth desensitizer drug products in § 354.65(c). Objecting to the warning in § 354.65(c)(1) that states, "Do not continue use beyond 2 weeks except under supervision of a dentist." All of the comments argued that 2 weeks is not an adequate trial period for the use of tooth desensitizers because the effectiveness of desensitizing agents may not be apparent after only 2 weeks of regular use. Two of the comments maintained that about 50 percent of the population does not regularly visit or have access to a dentist and, as a result, makes use of OTC medications. These comments stated that, in the absence of a dental recommendation, 4 weeks, rather than 2 weeks, is a more realistic trial period for the use of a tooth desensitizer. The comments stated that they were aware of the Panel's concern that a diagnosis of hypersensitivity may not accurately be made without professional advice, but contended that the majority of sufferers could make the association between inciting factors and the symptoms of hypersensitivity. One comment recommended that the agency combine § 354.65 (c)(1) and (c)(4) to read as follows: "If relief is not apparent after 4 weeks of regular use or if the intensity of pain increases, see your dentist, as this may indicate a serious dental problem." The other two comments suggested that § 354.65(c)(1) be revised to read as follows: "Do not continue use beyond 4 weeks in the absence of relief except as directed by a dentist. When used on a daily basis, a decrease in sensitivity should occur within the first 2 weeks and greater improvement will occur as regular use continues."

One comment requested that proposed § 354.65(c)(5), which states "See your dentist as soon as possible whether or not relief is obtained," be revised to read as follows: "If relief is not apparent after 4 weeks of regular use or if the intensity of pain increases, see your dentist, as this may indicate a serious dental problem." The comment maintained that if sensitivity is effectively reduced after 4 weeks, it is unnecessary for the consumer to consult a dentist. However, the comment added that if sensitivity is not reduced after 4 weeks, a dentist should be consulted as soon as possible because a dental problem may be present. One comment recommended replacing §§ 354.65 (c)(4) and (c)(5) with the following "Caution" statement: "Caution: Sensitive teeth may require professional attention. See your dentist if the problem persists or if irritation occurs." The other comment recommended a similar statement: "Caution: Sensitive teeth may require professional attention. See your dentist if the problem persists." Both comments contended that the two warnings proposed by the Panel (§ 354.65 (c)(4) and (c)(5)) are excessively and unnecessarily alarming and that the same purpose could be accomplished in a less alarming manner by using a caution statement similar to one recommended above.

The agency agrees with the comments that, when treating dental hypersensitivity with a tooth desensitizer, 4 weeks is a more reasonable trial period than 2 weeks. Clinical data submitted to the agency in support of the Category I status of potassium nitrate as a tooth desensitizer clearly demonstrate that hypersensitivity may be reduced after 2 weeks treatment, but the reduction increases steadily and is more apparent after 4 weeks treatment. (See comment 9 above.)

Although all of the comments maintained that hypersensitivity can be self-diagnosed and self-treated by the consumer, the agency believes that a professional diagnosis is necessary before using a tooth desensitizer for longer than 4 weeks. Dental hypersensitivity may have many causes including faulty restorations, cracked teeth, or infected dental pulp (47 FR 22712 at 22750). Because none of these conditions would be helped by a tooth desensitizer (47 FR 22750), the agency believes that a dentist's evaluation and treatment is necessary before using a tooth desensitizer for longer than 4 weeks. The agency agrees with the Panel that tooth desensitizers should be available as OTC drug products for temporary use until a dentist can be seen or for longer use under professional supervision (47 FR 22749). However, because hypersensitivity may be caused by conditions that require treatment by a dentist, the agency concludes that 4 weeks is an adequate period of time for a consumer to use a tooth desensitizer without professional advice even if the condition appears to improve.

The agency believes that the two warnings recommended by the Panel in §§ 354.65 (c)(4) and (c)(5) can be combined with the warning recommended in § 354.65(c)(1) and simplified into one warning which is proposed in § 356.62(c) as follows: "Sensitive teeth may indicate a serious

problem that may need prompt care by a dentist. See your dentist if the problem persists or worsens. Do not use this product longer than 4 weeks unless recommended by a dentist or doctor." The agency has determined that the signal word "warning" rather than the word "caution" will be used routinely in OTC drug labeling that is intended to alert consumers to potential safety problems. Therefore, the word "warning" will be used for the above statement in this proposal.

31. One comment objected to the Dental Panel's warnings recommended for tooth desensitizers in § 354.65(c)(3), "Children under 12 years of age should be supervised in the use of this product." The comment stated that the oral toxicity of these products is very low based on the amount of product used for normal daily toothbrushing (of which only 5 to 10 percent is actually ingested) or even if the entire tube were inappropriately ingested. The comment suggested that because tooth desensitizers present a minimal health risk to children upon ingestion during normal use and because dentinal hypersensitivity is primarily an adult condition, the warnings in §§ 354.65 (c)(2) and (c)(3) are not appropriate for tooth desensitizers and should be deleted.

Three comments recommended that the agency delete the Panel's recommended warning in § 354.65(c)(6), which states "If irritation persists, inflammation develops, or if fever and infection develop, discontinue use and see your dentist or physician promptly." Two comments contended that irritation, fever, and infection are not relevant to the condition of, or the products available for, sensitive teeth. Two comments suggested that this warning was unnecessarily alarming, and one of them added that the warning would contribute to the consumer's negation of label precautions because of their excessive use in unwarranted situations.

All three comments suggested that the Panel's recommended warning in § 354.56(c)(7), which states "Do not exceed recommended dosage," be deleted because dentifrice products have a universally accepted, standard method of use and that their safety, as a class, makes such a warning unnecessary. Two comments stated that the proposed warning appeared excessive for the dentifrice product category and should properly be reserved for those products that require it so as to avoid diluting the impact of the message, while one comment added that it is not possible or necessary to establish a "recommended dosage" for dentifrices.

The agency agrees with the comments that §§ 354.65 (c)(3), (c)(6), and (c)(7) are not necessary for the safe use of a tooth desensitizer drug product. The toxicity of the Category III tooth desensitizing agents discussed in the Panel's report is low (47 FR 22712 at 22751 to 22756) and products containing these ingredients are not likely to be used to any great extent by children under 12. Based upon the new directions proposed by the agency for tooth desensitizers stating that a dentist be consulted for use in children under 12 (see comment 38 below), the agency concludes that the warning "Children under 12 years of age should be supervised in the use of this product" is redundant.

The agency reviewed the Panel's evaluation of tooth desensitizing ingredients (47 FR 22750) and did not find any discussion that the consumer should consult a dentist or physician if fever, irritation, or infection are present. The agency does not consider fever, irritation, and infection as being related to dental hypersensitivity and, therefore, does not believe that a warning for the consumer to consult a dentist or physician if those symptoms are present is necessary on a tooth desensitizing drug product.

The agency concludes that the Panel's recommended warning in § 354.65(c)(7) "Do not exceed recommended dosage" can be deleted. The agency believes that consumers know how to use a dentifrice and that it is unnecessary as well as impractical to establish a recommended dosage for a dentifrice.

Therefore, the agency is not including the Panel's recommended §§ 354.65 (c)(3), (c)(6), and (c)(7) in this amendment.

32. Several comments disagreed with certain aspects of the directions (§ 354.50(d)) recommended by the Dental Panel for agents for the relief of toothache (47 FR 22712 at 22758). Noting that the proposed directions specify that the medication should be placed on a cotton pledget, the comments maintained that a cotton pledget is impractical for use with a gel, which is placed directly into a tooth cavity without cotton. Therefore, the directions should be modified to make it clear that they do not apply to gel formulations. One comment stated that the directions should be limited to eugenol (85 to 87 percent).

One comment argued that the directions that restrict use of a toothache relief medication to 1 minute not more than four times daily are inconsistent with the Panel's recommended testing requirements for these drugs, which state that the cotton pledget moistened with medication should be removed after 5 minutes. The comment added that the limitation on the frequency of application is impractical and unnecessary for this class of products, and that use of the drug should depend on patient requirements.

The agency acknowledges that the directions recommended by the Panel in § 354.50(d) may not be appropriate for all ingredients and/or formulations (such as gels). The directions (regarding use of a cotton pledget and limitation of use to 1 minute not more than four times daily) were written for products containing 85 to 87 percent eugenol, the only ingredient classified by the Panel as a Category I toothache relief agent. Eugenol can irritate oral mucous membranes; therefore, it is necessary to place eugenol on a cotton pledget in order to confine the drug to the tooth cavity, and prevent its spread to the oral tissues. Likewise, the 1-minute time limitation is necessary to prevent irritation. Eugenol is classified in Category III in this amendment (see comment 7 above). Because there are no Category I ingredients for the relief of toothache, no labeling for this use is included in this document. However, in the event that eugenol reaches monograph status, the agency is proposing to clarify part of the directions for eugenol to instruct the consumer to remove the cotton pledget. The revised directions would be as follows: "* * * Moisten a cotton pledget with 1 or 2 drops of medication and place in the cavity for approximately 1 minute and then remove * * *." As discussed below, if other ingredients for the relief of toothache are reclassified to Category I, the agency will propose directions that are appropriate for those ingredients.

The Panel recommended that eugenol be used not more than four times a day (47 FR 22712 at 22728). The comment did not submit any data in support of a more frequent interval of using eugenol; therefore, the agency has no basis for changing the Panel's recommendation. The agency also points out that products to relieve toothache are intended to be used only for a short time until a dentist can be seen. These products may provide some temporary relief, but the underlying cause of the toothache remains untreated. Unrestricted use of such products may tend to cause an individual to postpone a necessary visit to the dentist. Therefore, the agency believes that it is in the consumer's best interest for toothache relief agents to

have a limitation on their frequency of use.

33. One comment contended that the age limitations in the Panel's proposed dosage for benzocaine as an agent for the dental relief of toothache are in error (47 FR 22712 at 22730). The comment stated that the Panel must have intended that this drug be limited to use in individuals 12 years and older rather than the "2 years of age and older" as stated in the Panel's proposed dosage.

The agency does not believe that the Panel intended to limit the use of benzocaine to individuals 12 years of age and older in its proposed dosage for this ingredient as a toothache relief agent (47 FR 22730).The Panel recommended that agents for the relief of toothache are appropriate for use in children under 12 years of age when it stated that eugenol could be used in children 2 years of age and older (47 FR 22758). The Panel also determined that products containing benzocaine are safe for use in children under the age of 12 years when it recommended directions for the use of benzocaine as a teething preparation in infants 4 months of age or older (47 FR 22738).

The comment did not submit any data or present any rationale for limiting the use of benzocaine as an agent for the relief of toothache to individuals 12 years of age and older. Therefore, the agency concludes that the Panel's proposed dosage for benzocaine for use as an agent for the relief of toothache in children 2 years of age and older is appropriate and does not need to be revised.

34. One comment requested that a gel dosage form be included in the Dental Panel's proposed dosage for benzocaine for use as an agent for the relief of toothache (47 FR 22712 at 22730). The comment also explained that the use of a cotton pledget would not be appropriate for applying benzocaine in a gel dosage form to an open tooth cavity.

The agency believes that a gel dosage form may be appropriate for benzocaine used as an agent for the relief of toothache and agrees that the use of a cotton pledget to apply benzocaine in a gel dosage form to an open tooth cavity would not be necessary. However, the ingredient benzocaine remains in Category III for use as an agent for the relief of toothache in this amendment. (See comment 5 above.) Until sufficient data are submitted to reclassify this ingredient to Category I for use to relieve toothache pain, the agency is not able to proposed directions that would address the dosage form to be used.

35. One comment objected to the Dental Panel's recommendation that products containing butacaine sulfate be packaged in single-use units to contain no more than 30 milligrams (mg) of butacaine sulfate each with no more than six units per package (47 FR 22712 at 22719). The comment stated that to repackage its butacaine sulfate dental ointment (currently marketed as a 4-percent ointment in ¼ and 1 ounce (oz) tubes) to comply with the Panel's recommendations would create a number of problems, all contributing to increased production costs. The comment added that its present collapsible tube supplier has stated that it is not possible to provide a tube for only 0.75 g of this drug product and thus it would be necessary to change the package style. The comment stated that due to the characteristics of this product, the best packaging alternative available is a "form-fill-seal" pouch, for which suitable material needs to be identified. In addition, the comment stated that the size of the pouch, which needs to be determined, may be too small to permit printing of the required labeling, so that separate closures would have to be provided. The comment claimed that it did not have the capability in-house to solve those problems and, thus, the firm would be required to use a contract packager.

As an alternative to the Panel's proposed single-use unit package, the comment recommended that its currently marketed 1-oz tubes be discontinued and the package of six ¼-oz tubes be maintained. Each ¼-oz tube would provide 10 applications per tube using a 2-inch ribbon per application because the firm had determined in its laboratory that 30 mg is obtained by using this amount of its ointment from the ¼-oz tube. Thus, the comment recommended that the statement "apply not more than a two inch ribbon" be added to the directions section of the labeling for these products. The comment added that its product has been marketed for over 40 years with few reports of adverse reactions over the last 31 years, none of which were of a serious nature, and contended that its recommended packaging and directions for products containing butacaine sulfate rationally resolve the problem of package size limitations.

The agency has reviewed the adverse reaction reports that have been submitted for dental products containing butacaine sulfate (Ref. 1). A total of three adverse reactions have been reported. These reports do not support the Panel's recommendation to package and label 4 percent butacaine sulfate in single-use units containing no more than 0.75 g of the product with no more than six units per package. One woman had an allergic reaction to the drug which would not be unusual for a "caine" type of local anesthetic. Because of such allergic reactions, the Panel recommended, and the agency is proposing, the warning "Do not use this product if you have a history of allergy to local anesthetics such as procaine, butacaine, benzocaine, or other 'caine' anesthetics." One man experienced edema and developed an ulcer in the mouth while using the drug. This marketing history of only three relatively mild adverse reactions while butacinae sulfate has been marketed in a dental ointment without package size limitations supports the comment's contention that package size limitations supports the comment's contention that package size limitations are not necessary for the safe marketing of OTC drug products containing this ingredient. Therefore, the agency is not proposing package size limitations for butacaine sulfate in this tentative final monograph and is revising the directions for use for these products to delete reference to single-use packaging.

The agency is also deleting the Panel's warnings recommended specifically for butacaine sulfate in § 354.55(c)(4) of its proposed monograph because the information in these warnings is included in the directions for use for these products in § 356.52(d)(3) of this proposal. The Dental Panel's recommended direction "do not use more than one unit at a time (each unit to contain no more than 30 milligrams)" contains the substance of the comment's suggested phrase "apply not more than a two inch ribbon" without being product specific. Because the size of the opening of a particular container and the consistency of a particular drug product will affect the amount of drug delivered in a given "ribbon"-size of the product, the agency is revising the directions to require a dosage of 30 mg butacaine sulfate per application which is relevant to all drug products regardless of their consistency or the size of the package opening. The agency is also revising the directions for butacaine sulfate for clarity and to conform with the format of other OTC drug monographs to read "For products containing butacaine sulfate identified in § 356.12(c)—The product contains 30 milligrams butacaine sulfate per dosage unit. Adults: Apply (manufacturer should state specific amount of product that contains 30 milligrams butacaine sulfate) to the affected area. Do not apply again for at least 3 hours. do not use more than three applications in 24 hours unless directed by a dentist or doctor. Children under 12 years of age: Consult a dentist or doctor."

Reference

(1) Department of Health and Human Services, Food and Drug Administration, "Annual Adverse Reaction Summary Listing," pertinent pages for the years 1976 through 1990, in OTC Volume 13BTFM, Docket Number 80N-0226, Dockets Management Branch.

36. One comment objected to the Dental Panel's limitation of phenol-containing oral mucosal analgesic products to two categories, i.e., teething preparations and dental rinses. The comment stated that the other two Category I oral mucosal analgesics, benzocaine and butacaine sulfate, do not share this limitation. The comment expressed concern that products containing phenol would be restricted to a liquid dosage form, such as a dental rinse only, while products containing benzocaine and butacaine sulfate could be marketed in dosage forms other than dental rinses, such as sprays and gels. The comment stated that sprays and gels have been used for a long time by consumers and professionals for treating conditions requiring topical analgesia, that the Panel did not provide reasons why phenol was limited to teething preparations and dental rinses, and that, without scientific justification for this limitation, the tentative final monograph should provide for the continued use of phenol-containing sprays and gels.

Some of the ingredients, including phenol preparations, evaluated by the Dental Panel in its report on OTC relief of oral discomfort drug products were also evaluated by the oral Cavity panel in its report on OTC oral health care drug products (47 FR 22760) and by the agency in the first segment of the tentative final monograph for OTC oral health care drug products (53 FR 2436). Because of the similarities and overlap between these two rulemakings, the agency has decided to combine them. (See part II. paragraph B.1. below.) Therefore, the agency is amending the tentative final monograph for OTC oral health care drug products to include the ingredients and indications reviewed by the Dental Panel as OTC drug products for the relief of oral discomfort. Oral mucosal analgesic ingredients are being included as oral health care anesthetic/analgesic ingredients. (See part II. paragraph B.5. below.) The agency proposed directions for phenol preparations in § 356.55(d)(6)(i) (A) and (B) and § 356.55(d)(6)(ii) of the tentative final monograph for OTC oral health care drug products that provide for solid and nonsolid dosage forms and for direct application as well as for use as a mouthwash (oral rinse) (53 FR 2436 at 2459). The agency believes that these proposed directions answer the comment's concerns.

Because the first segment of the tentative final monograph for OTC oral health care drug products did not address teething preparations, the agency is amending the recommended directions for phenol preparations by adding the following directions for use in § 356.52(d)(7)(iii) of this proposal: "For products intended for use as a teething preparation, the product is an aqueous solution or suspension containing phenol or phenolate sodium equivalent to 0.5 percent phenol. For infants and children 4 months to under 12 years of age: Apply to the affected area. Use up to 6 times daily or as directed by a dentist or doctor."

37. One comment made several recommendations regarding the directions for use recommended by the Dental Panel for phenol preparations. It stated that the Panel's recommended directions for the use of phenol-containing oral mucosal analgesics fail to consider the differences in the appropriate dosage limitations between dental rinses and other dosage forms. The comment agreed with the Dental Panel's recommendation that the total daily dosage of phenol be limited to a maximum of 600 mg for adults and children 12 years of age and older, adding that this limitation is consistent with the maximum daily dosage for phenol-containing lozenges recommended by the Oral Cavity Panel (47 FR 22760 at 22928). However, the comment indicated that the Dental Panel's phrasing of the directions in § 354.55(d)(4) may lead one to believe that the daily dosage limitation applies to the amount of product that is used as a rinse rather than the amount of active ingredient that may be potentially ingested. The comment emphasized the importance of recognizing that the actual amount of product ingested represents only a small portion of the amount of liquid placed in the oral cavity. To support its statement, the comment submitted a number of studies concerning the volume of mouthrinse used under unsupervised conditions (Ref. 1), the maximum absorption of phenol (Ref. 2), and the duration of anesthesia (Refs. 3 through 6). Based on these studies, the comment stated that the maximum amount of phenol absorbed during rinsing of the mouth with a preparation containing 1.4 percent phenol is 12 percent; the maximum duration of anesthesia is 2 hours; and the mean volume of liquid used by the subjects to rinse the oral cavity is 16.5 milliliters (mL). According to the comment, if this volume of rinse is used every 2 hours "around-the-clock," the maximum amount of phenol ingested (348 mg) is well below the 600-mg limit recommended by both the Dental Panel and the Oral Cavity Panel for adults and children 12 years of age and older.

The comment also stated that age has no influence on the duration of topical anesthesia and that a dose frequency of every 2 hours is also appropriate for children 6 to 12 years of age. The comment suggested a volume limitation of 15 mL for this age group and stated that rinsing with 15 mL of 1.4 percent phenol every 2 hours "around-the-clock" could result in a maximum absorption of 25 mg of phenol per dose, which would not exceed the 300-mg total daily dose limit recommended by the Dental Panel for children 6 to under 12 years of age.

The comment further contended that the Dental Panel unnecessarily restricted the dose frequency for phenol-containing oral mucosal analgesic solutions to a maximum of six times per day. As an alternative, the comment recommended that the maximum single dosage for adults be set at 50 mg every 2 hours, stating that a 50-mg dose used at 2-hour intervals would comply with the maximum daily dosage of 600 mg phenol recommended by the Dental and Oral Cavity Panels. The comment submitted data to support its recommendations (Refs. 1 through 6). For children 6 to under 12 years of age, the comment stated that the maximum single dose should not exceed 25 mg of phenol with a 300-mg maximum daily dosage of phenol. The comment noted that these maximum dosage limits represent the quantity of phenol ingested and that it is highly unlikely that a consumer would use a product "around-the-clock" (for 24 hour), but if this did occur, the total daily dosage would still be within the acceptable safety limits.

The comment requested that § 354.55(d)(4) be revised to read as follows:

(4)(i) *For products containing phenol identified in § 354.12(c).* "Apply to (spray on) the affected area. Repeat every two hours if necessary."

(ii) *For products containing phenol identified in § 354.12(c) when used as a dental rinse.* "Rinse the affected area for approximately 15 seconds then expel remainder. Repeat every two hours if necessary."

Some of the ingredients, including phenol preparations, evaluated by the Dental Panel in its report on OTC relief of oral discomfort drug products were also evaluated by the Oral Cavity Panel in its report on OTC oral health care drug products (47 FR 22760) and by the agency in the first segment of the tentative final monograph for OTC oral

health care drug products (53 FR 2436). Because of the similarities and overlap between these two rulemakings, the agency has decided to combine them. See part II. paragraph B.1. below.) Therefore, the agency is amending the tentative final monograph for OTC oral health care drug products to include the ingredients and labeling reviewed by the Dental Panel as OTC drug products for the relief of oral discomfort. In this amendment, the agency is proposing to include oral mucosal analgesic ingredients and labeling in the anesthetic/analgesic sections of the oral health care drug products tentative final monograph. (See comment 36 above.)

The agency addressed many of the comment's concerns in the first segment of the tentative final monograph for OTC oral health care drug products and proposed directions for phenol preparations in § 356.55(d)(6)(i) (a) and (b) and § 356.55(d)(6)(ii) (53 FR 2436 at 2459). The agency discussed the following concerns expressed by the comment: for adults and children 12 years of age and over and for children ages 6 to under 12, a maximum daily dosage of phenol of 600 mg and 300 mg, respectively (53 FR 2440 and 2441); a 2-hour dosage frequency for the solid dosage form (10 to 50 mg of phenol) and for dosage forms other than solid (0.5 to 1.5 percent phenol) (53 FR 2440 and 2441); no restriction of rinsing volume for adults and children 12 years of age and over; a proposal for a 10 mL restriction of rinsing volume for children 6 to under 12 years of age (53 FR 2455); a rinsing time of at least 15 seconds for both adults and children 6 years of age and over; for direct application for adults and children 2 years of age and older, to allow the products to remain in place for at least 15 seconds (53 FR 2455), and to change the term "expel remainder" to "spit out" (53 FR 2438).

The agency believes that the above-referenced discussions and the proposed directions for phenol preparations in § 356.55(d)(6)(i) (a) and (b) and § 356.55(d)(6)(ii) in the first segment of the tentative final monograph for OTC oral health care drug products answer the comment's concerns.

The agency has reviewed the Dental Panel's recommended term "dental rinse" used in § 354.55(d)(4) and is proposing to change the term to "mouthwash (oral rinse)" in order to better describe the use of the product and to be consistent with the agency proposal in the first segment of the tentative final monograph for OTC oral health car drug products.

References

(1) Yankell, S.L., M.M. Dolan, and J. Pauls, "Mouthrinse Use Patterns," Journal of Preventive Dentistry, 5:28, 1978.

(2) Davis, C.S., "Oral Mucosal Absorption of Phenol from Chloraseptic Mouthwash and Gargle," draft of unpublished study, Comment C00013, docket No. 80N-0228, Dockets Management Branch.

(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) 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, Comment C00014, Docket No. 80N-0033, Dockets Management Branch.

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

38. Three comments objected to the directions proposed by the Dental Panel for tooth densensitizers in § 354.65(d). One comment stated that the sentence "For children under 2 years of age there is no recommended dosage except under the advice and supervision of a dentist or physician," is unnecessary. The comment reasoned that children under 2 years of age, whose teeth are erupting through the gum, would not use a densensitizing toothpaste because neither gingival recession nor periodontitis would be present for the period of time necessary to cause gum recession or tooth erosion which lead to dentinal hypersensitivity. The comment added that the statement "Children under 12 years of age should be supervised in the use of this product," is likewise unnecessary in the directions because the oral toxicity of tooth desensitizers is low, and only 5 to 10 percent of the toothpaste is ingested during actual brushing. The comment maintained that because dental hypersensitivity is primarily an adult condition, a health risk to children resulting from ingestion of a tooth desensitizer is highly unlikely under conditions of normal use. The other two comments stated that the directions are excessively wordy, considering the familiarity of users with the product category. They recommend the following directions: "Use in place of your regular toothpaste or as your dentist directs. Consult your dentist for use by children under 12 years of age."

The agency agrees with the comment that dental hypersensitivity is primarily an adult condition, that directions for use by children are unnecessary, and that these drug products need not be used in children unless directed by a dentist or doctor. Additionally, data submitted to the agency in support of the effectiveness of potassium nitrate as a tooth desensitizer (Refs. 1 and 2) (see also comment 8 above) indicate that at least a 1-inch strip of dentifrice should be used twice a day for optimum effectiveness. Based on the studies conducted, the consumer should be instructed to brush thoroughly for at least 1 minute so that the potassium nitrate is applied to all sensitive areas of the teeth. Further, because of the sensitivity of the teeth, the agency believes that it should be suggested to consumers that a soft bristle toothbrush be used to apply the dentifrice. Therefore, in this tentative final monograph, the agency is proposing in § 356.62(d) that the directions for tooth desensitizers read as follows: "Adults and children 12 years of age and older: Apply at least a 1-inch strip of the product onto a soft bristle toothbrush. Brush teeth thoroughly for at least 1 minute twice a day (morning and evening) or as recommended by a dentist or doctor. Make sure to brush all sensitive areas of the teeth. Children under 12 years of age: consult a dentist or doctor."

References

(1) Comment No. C00011, Docket No. 80N-0228, Dockets Management Branch.

(2) Comment No. C00012, Docket No. 80N-0228, Dockets Management Branch.

39. One comment requested that the oral mucosal analgesic portion of the tentative final monograph include a section on professional labeling. The comment noted that the Dental Panel classified certain indications for oral mucosal analgesics in Category II, specifically post-extraction pain and the pain of a gingivectomy. The comment agreed with the Panel that these indications are inappropriate for consumer labeling, but maintained that they are legitimate uses of local anesthetics by the dental professional. Requesting that the agency develop and include in the tentative final monograph acceptable labeling indications for use only in promotion to professionals, the comment suggested that such legitimate indications include claims for relief of pain associated with gingivectomy, insertion of immediate dentures, pericoronitis, aphthous ulcers, infectious stomatitis, Vincent's infection, tooth extraction and other oral surgery, and for preinjection topical anesthesia.

The agency believes that some of the comment's suggested indications for products containing topical anesthetic/

analgesic (oral mucosal analgesic) ingredients could be included in the professional labeling section of the monograph. The Dental Panel found that a combination of a topical anesthetic/analgesic and a denture adhesive is a rational combination because it may enable a denture wearer to benefit from the analgesic action, while the adhesive helps to secure the dentures, and both actions increase the comfort of the user (47 FR 22712 at 22721). The Panel stated that immediate dentures (dentures that are placed in the mouth immediately following the extraction of the natural teeth as part of the surgical procedure), particularly, may be uncomfortable or painful in some instances. The Dental Panel recommended benzocaine, butacaine sulfate, and phenol preparations (phenol and phenolate sodium) as Category I oral mucosal analgesics, but not for these professional uses.

Ship, Williams, and Osheroff (Ref. 1) report that topical anesthesia has been used, in dentistry, prior to injection of anesthetic drugs and for suppression of the gag reflex in oral manipulations. They studied the anesthetic potency and duration of effect of topically applied dyclonine hydrochloride when compared with lidocaine hydrochloride and four antihistamines. Test solutions were applied with cotton-tipped applicator sticks or as a mouth wash to affected areas. Fifteen patients with severe, recurrent aphthous stomatitis were evaluated over a 6-month period. The results showed excellent depth of anesthesia when 0.5 to 5 percent dyclonine hydrochloride was compared with 5 percent lidocaine hydrochloride. The mean duration of anesthesia was 45 minutes for dyclonine hydrochloride with onset occurring in 4 to 8 minutes. No perceptible differences were noted in the depth of anesthesia produced by the various concentrations tested. No adverse reactions were reported. The mean duration of anesthesia was 30 minutes for lidocaine hydrochloride, with onset occurring in 3 to 8 minutes.

Ping, White, and Spear (Ref. 2) discussed the use of dyclonine hydrochloride to control the severe gag reflex which they considered necessary to facilitate intraoral dental radiographs. Dyclonine hydrochloride was used in more than 300 patients during a 16-month period. Patients rinsed their mouths with 0.5 to 1 percent dyclonine solution for 40 seconds and then expectorated. After a short period of time, full mouth periapical dental radiographs were taken with complete absence of the gag reflex. No appreciable increase in the effectiveness of the more concentrated dyclonine solution could be detected. Patients rinsing their mouths with dyclonine solution before intraoral radiographs experienced every little discomfort, resulting in better radiographs. The authors noted that, in prosthodontics, the gag reflex also presents frequent problems during the making of impressions. The authors reported that dyclonine mouth rinses gave excellent results, but only a few patients were studied. However, the extent and duration of anesthesia were considered unnecessarily extensive for the average case. The agency lacks sufficient data to ascertain whether anesthetic/analgesic drugs like dyclonine are currently used in prosthodontic procedures and invites comments and data on such use.

Adriani and Zepernick (Ref. 3) compared the potency and effectiveness of dyclonine hydrochloride with other topical anesthetics in man by using electrical current delivered by a nerve stimulator. Their procedure involved quantitating the amount of electric current needed to elicit a response after the topical application of 1 percent dyclonine hydrochloride to a mucosal surface. Several surfaces were studied, with the tip of the tongue used for most studies because of its sensitivity, accessibility, and production of the most consistent results. When the duration and effectiveness were considered on a milligram for milligram basis in the study, the results showed good depth of anesthesia when 1 percent dyclonine hydrochloride was compared with 4 percent lidocaine and 6 percent hexylcaine. The authors specifically mentioned that 1 percent dyclonine hydrochloride is an effective topical anesthetic that does not have adverse systemic responses characteristic of other local anesthetics.

Based on the above data, the agency believes that dyclonine hydrochloride can be used for the relief of discomfort in patients with an excessive gag reflex when having impressions of the teeth made or during intraoral radiography and for preinjection topical anesthesia under the supervision of a dentist or physician. However, the agency lacks adequate data to support the use of dyclonine hydrochloride for the relief of pain associated with gingivectomy, insertion of immediate dentures, or tooth extraction and the use of benzocaine, butacaine sulfate, or phenol preparations (phenol and phenolate sodium) for any of the above uses. Accordingly, the agency is amending the section on professional labeling that was proposed for oral anesthetic/analgesic ingredients in the first segment of the tentative final monograph for OTC oral health care drug products, § 356.80, to enable manufacturers to provide health care professionals with information about the additional indications for products containing the ingredient dyclonine hydrochloride. However, these indications cannot be used on the consumer labeling of the product because consumers cannot self-diagnose and self-treat these conditions.

The agency is proposing the following indications for products containing dyclonine hydrochloride in the professional labeling section of this amendment: "For the temporary relief of discomfort in patients with an excessive gag reflex when having impressions of the teeth made or during intraoral radiography" and "For use as a pre-injection topical anesthetic on the oral mucosa."

Concerning the comment's suggested claims for relief of pain associated with "other oral surgery," the agency does not find a sufficient basis to include this indication in the professional labeling for topical anesthetic/analgesic drug products. The agency believes that the term "other oral surgery" is ambiguous and could imply that these topical products may have an anesthetic effect on deeper tissues than would be affected by the superficial anesthetic effect of topical anesthetic/analgesic drug products.

In the first segment of the tentative final monograph for OTC oral health care drug products, the agency determined that anesthetic/analgesic drug products can be used for the relief of pain associated with tonsilitis, pharyngitis, stomatitis, and throat infections which first must be diagnosed by a dentist or doctor (53 FR 2436 at 2438 and 2439). Therefore, "stomatitis" is included in this amendment as a professional indication for oral anesthetic/analgesic ingredients. Likewise, the agency believes that the pain associated with Vincent's infection (necrotizing ulcerative gingivitis or trench mouth) could be alleviated by OTC anesthetic/analgesic ingredients after diagnosis by a dentist or doctor. Therefore, the agency is amending the professional labeling in § 356.80(a) to include "Vincent's infection."

Regarding the conditions of "aphthous ulcers" (canker sores) and "pericoronitis" (inflammation of the gingiva surrounding the crown of a partially erupted tooth, i.e., teething pain) mentioned by the comment, the Panel recommended these as OTC indications in § 354.55(b), and the agency has determined that these conditions are self-diagnosable and self-

treatable. Accordingly, the agency is proposing the OTC indication "For temporary relief of pain associated with canker sores" for all Category I oral mucosal analgesic ingredients and the OTC indication "For the temporary relief of sore gums due to teething in infants and children 4 months of age and older" only for benzocaine and phenol, for the reasons discussed above. (See comments 23 and 36 above.)

References

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(2) Ping, R. S., J. G. White, and L. B. Spear, "Dyclonine Hydrochloride as a Topical Anesthetic in Dentistry," Oral Surgery, Oral Medicine, and Oral Pathology, 10:623–626, 1957.

(3) Adriani, J., and R. Zepernick, "Clinical Effectiveness of Drugs Used for Topical Anesthesia," Journal of the American Medical Association, 188:711–716, 1964.

E. Comments on Combination Drug Products

40. Several comments objected to the Dental Panel's Category III classification of combinations containing two agents for the relief of oral discomfort from the same pharmacotherapeutic group, but with different mechanisms of action (47 FR 22712 at 22722). The comments contended that this Category III classification is inconsistent with recommendations made by the Topical Analgesic Panel and the Oral Cavity Panel that a combination of the topical analgesics phenol and benzocaine be Category I. Noting that phenol has a slow onset but a long duration of action as a topical analgesic, and that benzocaine has a rapid onset but a short duration of action as a topical analgesic, the comments argued that these differing pharmacologic activities for benzocaine and phenol supplement one another. Two of the comments added that further testing of the combination of these ingredients is unwarranted because both ingredients have well-defined actions. The comments requested that the combination of phenol and benzocaine be a Category I combination for use as an oral mucosal analgesic.

The agency agrees with the comments that the combination of benzocaine and phenol can be classified Category I for the relief of oral discomfort. In the first segment of the tentative final monograph for OTC oral health care drug products (53 FR 2436 at 2450 and 2451), the agency determined that the combination of benzocaine and phenol (i.e, oral anesthetic/analgesic ingredients) conforms to the requirements in 21 CFR 330.10 and to the agency's guidelines for OTC drug combination products (Ref. 1) and proposed Category I status. Because oral mucosal analgesics (e.g., benzocaine and phenol) are being combined with oral anesthetic/analgesics (See Part II. paragraph B.5 below), the combination of benzocaine and phenol is likewise proposed as Category I in this amendment.

Reference

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

41. Two comments stated that the Panel's Category II classification of combinations containing more than two Category I dentifrice and dental care agent active ingredients in section II. Paragraph D.6.e. of the May 25, 1982 advance notice of proposed rulemaking (47 FR 22712 at 22721) conflicts with the Panel's Category I classification of a three-ingredient combination containing an oral mucosal protectant, an oral mucosal analgesic, and an oral antiseptic (47 FR 22720 to 22721). One of the comments recommended that the agency make an exception for this particular three-ingredient combination and modify the Panel's recommendations accordingly. The second comment suggested that there be no limit to three active ingredients in combination and that combinations of two or more active ingredients be permitted provided they are sound and can be shown to be of value.

The agency agrees with the second comment that three-ingredient combinations need not be limited provided they are supported by adequate data. Moreover, FDA agrees that no fixed limit need be placed upon the number of active ingredients in a combination product if it can be shown to be a rational, safe, and effective combination with a suitable target population. This position is consistent with the FDA policy for OTC drug combination products in 21 CFR 330.10(a)(4)(iv) and with the guidelines for OTC drug combination products (Ref. 1). The various panels placed certain two- and three-ingredient combination products in Category I because data were presented to support their safety and effectiveness. Regardless of the number of ingredients, the agency will consider any combination for Category I that meets the regulation and guidelines mentioned above. The proposed allowable combinations are listed in § 356.20 of the amendment.

Reference

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

42. One comment stated that part of the Dental Panel's rationale for placing the combination of an oral mucosal protectant and a denture adhesive in Category II was not totally accurate. The Panel had stated that the thickness of the film of the protectant would interfere with the fit of the dentures (47 FR 22712 at 22722). The comment, however, explained that the film would probably not be thick enough to interfere with denture fit and suggested that a more appropriate rationale would be that the oral mucosal protectant "is not needed because the denture already covers the wound."

The agency agrees with the Panel's rational that the oral mucosal protectant would interfere with the action of the denture adhesive and that the added thickness of the protectant would interfere with the fit of dentures. The agency also accepts the comment's suggested rationale that the oral mucosal protectant is not needed in a product intended for use with dentures because the denture already covers the wound.

43. One comment disagreed with the Dental Panel's Category III classification for the combination of an oral mucosal protectant with an oral mucosal analgesic claiming a prolonged duration of action (47 FR 22712 at 22722 to 22723). The comment stated that the Panel was not aware that the prolonged action of benzocaine in an oral mucosal protectant paste had been documented. The comment briefly summarized: (1) the reported persistence of mucosal anesthesia by benzocaine when dissolved in an emollient dental past (Ref. 1), (2) the safety and effectiveness of this combination (Ref. 2), and (3) the prolonged retention of the paste in various parts of the mouth (Refs. 3, 4, and 5). Stating that the "oral mucosal protectant paste" with benzocaine is a marketed product that has been "Accepted" by the American Dental Association's Council on Dental Therapeutics since 1973, the comment added that a "prolonged action" claim is approved for advertising in the Journal of the American Dental Association and submitted a copy of the advertisement (Ref. 6). The comment concluded by strongly urging FDA to reverse the Dental Panel's position on the

"prolonged duration of action" claim for this marketed oral mucosal paste containing benzocaine and to reclassify this claim to Category I for this combination.

The agency has evaluated the data submitted by the comment and concludes that they are not sufficient to support the claim of a prolonged analgesic action for benzocaine when combined with an oral mucosal protectant. Some of the data (Refs. 3, 4, and 5) indicate that the duration of maintenance of the protectant paste in various regions of the mouth averaged 1 to 2 hours, depending on the region of the mouth to which the paste was applied. A wide range of times has been reported—from 10 minutes to 24 hours (Ref. 5). However, benzocaine was not included in the paste in these studies.

In one study in which benzocaine was included in the paste (ref. 1), the investigator reported that the onset of anesthesia, for the investigated group, varied between 10 to 20 minutes and persisted for 1 to 2 hours, but benzocaine in a nonprotectant paste was not included in the study. Therefore, there is no way of determining from this study whether the use of the protectant paste prolonged the duration of action of the benzocaine. In the other study in which benzocaine was included in the protectant paste (Ref. 2), the effectiveness of the benzocaine-protectant paste combination was compared with the effectiveness of the protectant paste alone in reducing the pain and discomfort associated with lesions of the oral mucosa. The results showed that the combination product was significantly more effective than the protectant paste in reducing the pain caused by the mucosal lesions.

While the results support the effectiveness of benzocaine as a Category I oral mucosal analgesic (which is the conclusion that the Panel reached), they do not demonstrate "prolonged duration of action" of the combination product compared with the oral mucosal analgesic without an oral mucosal protectant. Thus, the submitted studies are inadequate because they do not demonstrate that the combination of ingredients prolongs the analgesic effect of the oral mucosal analgesic. Studies must be designed and conducted to test the duration of the analgesic effect of the combination against its oral mucosal analgesic component alone in a nonprotectant vehicle, thus establishing that the oral mucosal protectant prolongs the duration of action of the oral mucosal analgesic.

The agency notes that the marketed protectant paste discussed in the studies (Refs. 1 through 5) was submitted to the Oral Cavity Panel (Ref. 7), but was not submitted to the Dental Panel for evaluation as a drug for the relief of oral discomfort. The ingredients in the paste, i.e., pectin, gelatin, and sodium carboxymethylcellulose in a plasticized hydrocarbon gel of 5 percent polyethylene in mineral oil, were not evaluated by the Oral Cavity Panel as oral mucosal protectants. The pectin and gelatin were evaluated as demulcents (47 FR 22760 at 22916 to 22919), and the sodium carboxymethylcellulose and plasticized hydrocarbon gel (polyethylene in mineral oil) were considered inactive ingredients (47 FR 22764). Thus, none of these ingredients is generally recognized as a safe and effective oral mucosal protectant.

Concerning the advertisement submitted by the comment, the acceptance of an advertisement for an OTC drug product in a scientific journal cannot be interpreted as signifying that the OTC drug or any claim made for it is generally recognized as safe and effective by the agency. The Federal Trade Commission has the primary responsibility for regulating OTC drug advertising. FDA does, however, regulate OTC drug advertising that constitutes labeling under the act. For an OTC drug to be generally recognized as safe and effective and not misbranded, the advertising for the drug product must satisfy the FDA regulations in § 330.1(d) (21 CFR 330.1(d)), which state that the advertising may prescribe, recommend, or suggest the drug's use only under the conditions stated in the labeling.

In conclusion, the agency concurs with the Panel and is proposing that the combination of an oral mucosal protectant with an oral mucosal analgesic claiming a prolonged duration of action for the analgesic be classified as Category III.

References

(1) Gaynor, H.M., "Clinical Investigation of the Use of Benzocaine in Orabase," Journal of Connecticut State Dental Association, 42:112–116, 1968.

(2) Stallard, R.E., N. Hiep, and A.K. ElGeneidy, "Safety and Effectiveness of Orabase with Benzocaine," draft of unpublished study, Comment No. C00016, Docket No. 80N–0228, Dockets Management Branch.

(3) Morgan, P.S., "An Oral Adhesive Vehicle in the Postoperative Care of Dental Extractions," Texas Dental Journal, 78:3–7, 1960.

(4) Kutscher, A.H., et al., "A New, Long-Lasting Vehicle for the Application of Drugs to the Oral Mucous Membranes," Journal of the American Dental Association, 62:40–43, 1961

(5) Parker, D. A. S., "Clinical Trial of an Oral Adhesive Paste," Australian Dental Journal, 13:197–200, 1968.

(6) Comment No. C00016, Docket No. 80N–0228, Dockets Management Branch.

(7) OTC Volume 130004.

44. One comment disagreed with the Dental Panel's recommendation that a combination drug product containing benzocaine and eugenol be placed in Category III for the relief of toothache. The comment submitted data from two short studies and claimed that the results confirm that a combination of benzocaine and eugenol in a beeswax dosage form is effective as a toothache remedy (Ref. 1). The comment acknowledged that no statistical evaluation of the data was performed and that, because of limited resources, the studies would not be expanded to a full clinical evaluation. Based on the data presented, the comment requested that the combination of benzocaine and eugenol be categorized as generally recognized as safe and effective as an agent for the relief of toothache.

The agency has reviewed the data from the two studies and has determined that insufficient information is provided to evaluate the results of the studies. There is inadequate information concerning the conditions under which the studies were conducted, the methods used to randomly allocate the test and control medications, and the category scales for determining pain intensity. In addition, the design of the studies was inadequate for determining that the combination is equal to or better than each of the active ingredients used alone at its therapeutic dose. The activity of the combination was only tested against a placebo preparation that consisted of the gum base without any active ingredients. The effectiveness of the combination should also have been tested against each individual ingredient separately in order to determine the contribution of each individual ingredient to the combination's activity. When the study was expanded to include an experimental formulation containing eugenol, the eugenol was present at twice the concentration contained in the combination product. These data are not adequate to establish effectiveness of the combination product.

The agency concurs with the Dental Panel's Category III recommendation for the combination of benzocaine and eugenol and is so classifying that combination in this tentative final monograph. The Panel placed benzocaine in Category III as an agent for the relief of toothache on the basis of insufficient effectiveness data (47 FR

22712 at 22730), and adequate data have not been presented to establish that benzocaine is effective in relieving toothache pain (see comment 5 above). Although the Panel placed eugenol in Category I for the relief of toothache, the agency has determined that the data are inadequate to demonstrate the effectiveness of eugenol for this use and is placing it in Category III (see comment 7 above). The agency invites the submission of data from well-designed, adequately-controlled studies that show benzocaine or eugenol as single active ingredients or in combination with each other are effective in reducing toothache pain.

Reference

(1) Comment C00006, Docket No. 80N-0228, Dockets Management Branch.

45. One comment expressed concerns about the categorization of the combination of benzocaine and capsicum and the combination of oxyquinoline, benzocaine, and capsicum for use in a dental poultice for the temporary relief of noncavity toothache.

The agency agrees with the Dental Panel that the combination of an oral mucosal analgesic (benzocaine) and a counterirritant (capsicum) is Category III for the relief of noncavity toothache pain (47 FR 22712 at 22722). The agency also agrees with the Panel's Category I classification of benzocaine (5 to 20 percent for use as an oral mucosal analgesic (47 FR 22725 and 22757 to 22758) and its Category III classification of capsicum, equivalent to 0.01 to 0.02 percent capsaicin, for use on intact (normal) oral mucosa as a counterirritant for the relief of toothache (47 FR 22731). The Panel stated that "If a Category III active ingredient or other condition is present in a combination product containing no Category II ingredient or labeling, the combination is classified as Category III" (47 FR 22722).

In addition, the requirements for OTC combination drug products, set forth in § 330.10(a)(4)(iv) [21 CFR 330.10(a)(4)(iv)] state that "an OTC drug may combine two or more safe and effective ingredients and may be generally recognized as safe and effective * * *." Category II or Category III active ingredients are not permitted in a Category I combination product. Therefore, if benzocaine is used as an oral mucosal analgesic in combination with a Category III ingredient (capsicum), the resulting combination is classified as a Category III product. One product containing benzocaine and capsicum was submitted to the Dental Panel. However, the submissions did not contain adequate data for the individual ingredients nor any data for the combination product (Refs. 1 and 2). Furthermore, the comment did not submit any new data to support the effectiveness of the combination of benzocaine and capsicum for the relief of noncavity toothache.

The agency has reviewed the labeling of the product containing benzocaine, capsicum, and oxyquinoline that was submitted to the Panel (Ref. 3) and determined that the benzocaine is included in the product as an oral mucosal analgesic, the capsicum as a counterirritant, and the oxyquinoline as an antimicrobial (antiseptic). The agency is proposing that this combination of ingredients in a dental poultice dosage form for the relief of noncavity toothache be placed in Category II. The Dental Panel classified combination products containing a counterirritant and an oral antiseptic (e.g., oxyquinoline) in Category II because it found no rationale for a combination product containing a counterirritant and an oral antiseptic (47 FR 22712 at 22722).

The Dental Panel deferred the review of oxyquinoline as an antiseptic to the Advisory Review Panel on OTC Oral Cavity Drug Products (47 FR 22715). The Oral Cavity Panel classified oxyquinoline in Category III as an antimicrobial ingredient for topical use on the mucous membranes of the mouth and throat because of insufficient safety data and no data from controlled in vivo studies on its effectiveness as a broad-spectrum antimicrobial agent (47 FR 22760 at 22880 to 22881). Despite the Oral Cavity Panel's Category III recommendation for oxyquinoline as a single ingredient, the agency concurs with the Dental Panel's recommendation that the combination of a counterirritant and an oral antiseptic should be in Category II. A counterirritant should be applied only "on intact (normal)" oral mucosa (47 FR 22731). Because no infection should be present at the site of use, no antiseptic is necessary. Accordingly, the agency is proposing that the combination of oxyquinoline, benzocaine, and capsicum be classified as Category II.

References

(1) OTC Volume 080191.
(2) OTC Volume 080214.
(3) OTC Volume 080003.

46. Expressing concern about the status of chlorobutanol in its company's toothache relief product that contains a combination of eugenol and chlorobutanol, one comment stated that consumers have commented favorably on the product. The comment contended that long time public usage and acceptance should be considered in the evaluation of such products and that small companies should not be expected to conduct elaborate tests on their products to prove effectiveness.

Although the Dental Panel placed eugenol in Category I for the relief of toothache (47 FR 22712 at 22727), the agency has determined that the data are inadequate to demonstrate the effectiveness of eugenol for this use and is placing it in Category III in this document (see comment 7 above). Chlorobutanol was not reviewed by the Panel. In the company's submission to the Panel (Ref. 1), chlorobutanol hydrous (chloroform derivative) was listed as an active ingredient on the product's label; however, chlorobutanol was not listed in the typed list of active ingredients in the submission nor were data submitted on chlorobutanol for any use. Thus, the Panel did not consider this ingredient to be an active ingredient and did not classify it. Adequate data demonstrating safety and effectiveness are necessary to support the use of this ingredient in toothache relief products. Without such data, the agency considers chlorobutanol a Category II ingredient for the relief of toothache.

FDA's standards for the effectiveness of OTC drugs in 21 CFR 330.10(a)(4)(ii) state that marketing experience and testimonials alone are not adequate proof of effectiveness, which is to be demonstrated by clinical studies. With regard to the comment's concern about impacts of testing on small manufacturers, this issue is discussed in comment 2 above.

Reference

(1) OTC Volume 080003.

47. One comment requested that a combination dentifrice containing 5 percent potassium nitrate and an acceptable Category I fluoride be classified as Category I for the combined indication of tooth desensitizing and dental caries control, provided that the product satisfies the Laboratory Testing Profile (LTP) criteria required for fluoride-containing anticaries dentifrices. Stating that data submitted to the agency adequately support a Category I classification of potassium nitrate as a tooth desensitizer, the comment maintained that a potassium nitrate/fluoride combination fully agrees with the criteria for Category I combinations cited by the Dental Panel in its report on OTC drug products for the relief of oral

discomfort (47 FR 22712 at 22720). Those criteria are as follows:

Two Category I active ingredients from different pharmacotherapeutic groups may be combined to treat different symptoms concurrently if each Category I active ingredient is present within its established dosage range; the combination is rational; there is a significant target population that suffers the concurrent symptoms; and the combination is as safe and as effective as each individual active ingredient used alone.

The comment noted the Category I status of fluorides for use in dentifrices for the prevention of dental caries and the major significance to the field of dental health of the effectiveness of the fluoride ion in lowering the incidence of dental caries. The comment maintained that a combination product containing a desensitizing agent and an anticaries agent would benefit those consumers who must use a desensitizing dentifrice because the combination would permit continued topical fluoride administration while the consumer is building and maintaining resistance to dental hypersensitivity. The comment added that the target population for the combination dentifrice consists of all consumers who have hypersensitive dentin, which is about 12 percent of the United States adult (18 or over) population or more than 19 million people.

Stating that it was unaware of any synergistic toxicity that could arise from the combination of fluoride and potassium nitrate, the comment maintained that the fluoride/potassium nitrate combination drug product should be as safe as the single ingredient dentifrices. The comment submitted toxicological data to confirm the safety of the combination product formulation (Refs. 1 and 2).

The comment maintained that the effectiveness of potassium nitrate as a desensitizing ingredient would not be expected to be diminished in the presence of fluoride. Citing the Merck Index, the comment noted that potassium nitrate is a very soluble inorganic salt, 1 g dissolving in 2.8 mL water (Ref. 3). Therefore, the comment contended that potassium nitrate would readily dissolve and saturate saliva to provide bioavailable nitrate at a level adequate for therapeutic effect, regardless of the presence of fluoride in the formula. The comment submitted in vitro data to support the bioavailability of the nitrate ion in dentifrices containing fluoride and potassium nitrate (Ref. 1). The comment also submitted two human dental hypersensitivity clinical studies (Refs. 4 through 7) to support its contentions regarding the effectiveness of the potassium nitrate/fluoride combination drug product.

The comment noted that the LTP's recommended by the Dental Panel in its report on OTC anticaries drug products (45 FR 20666 at 20677 to 20681) can be used to demonstrate the effectiveness of the fluoride ingredient in a fluoride/potassium nitrate combination drug product in place of extensive clinical testing. The comment submitted data to support the bioavailability of the fluoride ion in a fluoride/potassium nitrate combination dentifrice (Refs. 1 and 2) and data pertaining to the remineralization enhancement of teeth by dentifrices containing potassium nitrate and fluoride in combinations (Ref. 8).

The comment also submitted statements from four experts, including three former members of the Dental Panel, who reviewed the material submitted to the FDA by the comment and concluded that two currently available dentifrices containing potassium nitrate in combination with fluoride are generally recognized as safe and effective and not misbranded for the prevention of dental caries and the treatment of dentinal hypersensitivity (Ref. 9).

The comment recommended that FDA revise the Panel's recommendation in § 354.20, "Permitted combinations of active ingredients," by adding paragraph (f) as follows: "(f) Potassium nitrate 5% tooth desensitizer as identified in section 354.16 and any generally recognized as safe and effective fluoride-containing anticaries drug product."

The agency is proposing a Category I classification for potassium nitrate as a tooth desensitizing ingredient in this document (see comment 8 above), and has proposed a Category I classification for several fluoride ingredients as anticaries agents in the tentative final monograph for OTC anticaries drug products published in the **Federal Register** of September 30, 1985 (50 FR 39854 at 39872).

The agency agrees with the comment that a combination dentifrice containing 5 percent potassium nitrate and a Category I fluoride is a rational combination. Furthermore, the agency concludes that the submitted data support the safety and effectiveness of this combination.

The first study (Refs. 4, 5, and 6) was a 12-week, double-blind, 3-way comparative parallel investigation of one dentifrice containing 5 percent potassium nitrate combined with 0.76 percent sodium monofluorophosphate, one dentifrice containing 5 percent potassium nitrate alone, and one dentifrice base with no active ingredients (the placebo). The study was designed to measure the effect of these dentifrices on hypersensitive teeth. The primary study parameters were subjective assessments by the participants, tactile sensitivity scores (measured by the Yeaple probe device), and recorded responses to a preset cold air stimulus (a 1-second blast of air at 60 pounds per square inch and 65 to 70 °F from an air syringe). A total of 68 subjects with dentinal hypersensitivity were randomly assigned to one of the three groups and subsequently completed the 12-week course of treatment. Following baseline assessments, the subjects were observed at intervals of 2, 4, 8, and 12 weeks. Mean scores of all groups demonstrated progressive improvement throughout the 12 weeks of the trial. Improvement in scores occurred more rapidly with the two test dentifrices than with the placebo. By the end of the 12-week study period, the scores of those subjects using the potassium nitrate/sodium monofluorophosphate and the potassium nitrate dentifrices were roughly equivalent and significantly better than those of the subjects using the placebo dentifrice ($p \leq 0.001$). However, the study failed to compare the effects of the combination product against the desensitizing effects of sodium monofluorophosphate dentifrice alone. Thus, this study does not eliminate the possibility that fluoride preparations, which the Dental Panel classified as Category III tooth desensitizers (47 FR 22712 at 22751), are potentially effective for hypersensitivity treatment and that the sodium monofluorophosphate contributes to the desensitizing effect of the combination drug product.

The second study (Refs. 5, 6, and 7) was designed as a 12-week, 4-way, parallel, double-blind trial of four treatment dentifrices. One dentifrice contained 5 percent potassium nitrate and 0.76 percent monofluorophosphate, one contained 5 percent potassium nitrate as the single active ingredient, one contained 0.76 percent sodium monofluorophosphate as the single active ingredient, and the placebo dentifrice was composed of the dentifrice base with no active ingredients. As in the first study, the primary effectiveness parameters were subjective assessments by the participants, tactile sensitivity scores, and cold air stimulus scores. However, although the first study measured a subjective response to a preset blast of

cold air, the cold air scores in the second study were based upon incremental tolerance to a thermally adjusted stream of increasingly cooler air. A total of 60 subjects completed the study. As in the previous study, the potassium nitrate/sodium monofluorophosphate and the potassium nitrate dentifrices demonstrated similar levels of effectiveness in reducing tooth hypersensitivity. At the 2-week interval, both tactile and cold air scores for groups receiving the potassium nitrate containing dentifrices showed greater improvements than did corresponding scores for either the sodium monofluorophosphate or the placebo dentifrices. By the fourth week, the subjective assessments also demonstrated the greater effectiveness of the potassium nitrate products.

Although the tooth hypersensitivity scores of all groups decreased throughout the period of the trial, subjective, tactile, and cold air scores indicated that the potassium nitrate and the potassium nitrate/sodium monofluorophosphate dentifrices provided greater benefit than did the sodium monofluorophosphate or placebo dentifrices. Results of statistical tests of 12-week differences in mean subjective and tactile scores indicated highly significant differences ($p<0.01$) in favor of the potassium nitrate containing dentifrices when compared to the placebo. Tests of the cold air scores, however, in spite of noted differences, did not demonstrate the same high level of statistical significance ($p=0.08$ for the pairwise comparison of the potassium nitrate/sodium monofluorophosphate dentifrice against the placebo, and $p=0.05$ for the potassium nitrate dentifrice compared to the placebo). Subjective and tactile score comparisons at the 12-week interval of the potassium nitrate/sodium monofluorophosphate and the potassium nitrate dentifrices against the sodium monofluorophosphate dentifice were highly significant ($p<0.01$), while p-values for the 12-week cold air score comparisons of the sodium monofluorophosphate dentifrice and the two potassium nitrate products were somewhat higher (0.06 against the potassium nitrate/sodium monofluorophosphate dentifrice, and 0.04 versus the potassium nitrate dentifrice). The statistical tests indicated that there was no difference at week 12 in comparisons of the group scores of the sodium monofluorophosphate dentifrice versus the placebo and of the potassium nitrate/sodium monofluorophosphate dentifrice versus the potassium nitrate dentifrice.

These two studies produced consistent results indicating that the potassium nitrate/sodium monofluorophosphate and the potassium nitrate dentifrices are more effective tooth desensitizers than a placebo dentifrice and that the two test dentifrices provided similar therapeutic effects over a 12-week test period. The second study, in which an additional group received the fluoride dentifrice, demonstrates that after 12 weeks there is very little desensitizing benefit derived from either the placebo or the sodium monofluorophosphate dentifrice. Results from both studies indicate that the benefit derived from the two potassium nitrate products (with and without the sodium monofluorophosphate) is nearly the same, and results from the second study demonstrate that the difference in benefit derived from the sodium monofluorophosphate product compared to the placebo is not statistically significant after 12 weeks of continuous use. This evidence supports the conclusion that sodium monofluorophosphate does not contribute substantially to the effective, 12-week desensitizing relief derived from the combination dentifrice containing potassium nitrate and sodium monofluorophosphate.

When evaluating ingredients for their tooth desensitizing effectiveness, the Dental Plan considered fluoride preparations, including sodium fluoride, sodium monofluorophosphate, and stannous fluoride, as a group. It stated that "Since the availability of the fluoride ion is similar in all these preparations, it would suggest that the effectiveness data are also related in a similar manner" (47 FR 22712 and 22752). Therefore, the agency believes that since monofluorophosphate does not contribute to the desensitizing effect of the potassium nitrate/sodium monofluorophosphate dentifrice, other Category I fluoride ingredients would likewise not contribute to the desensitizing effect of a combination desensitizing/anticaries dentifrice.

Regarding the anticaries effectiveness of the sodium monofluorophosphate portion of this combination dentifrice, in its report on OTC anticaries drug products published in the **Federal Register** of March 28, 1980, the Dental Panel recommended LTP's Category I anticaries ingredients in dentifrice formulations (45 FR 20666 at 20677). The Panel stated that the extensive amount of testing of anticaries dentifrices, which has included laboratory animal testing and clinical testing, allows prediction as to which dentifrice formulations will be effective. The Panel concluded that, if certain analytic and biologic tests are conducted on new formulations and acceptable test values are achieved, clinical testing of those formulations is not required. The analytic tests recommended by the Panel were theoretical total fluorine determination, available fluoride ion determination, pH, and specific gravity. The Panel also recommended that fluoride dentifrices meet the requirements of two of the following biologic tests: (1) Enamel solubility reduction; (2) fluoride uptake by enamel; and (3) animal caries reduction.

Because these LTP's represented a new concept with many technical issues yet to be resolved, they were not included in the Panel's proposed monograph or in the agency's first segment of the tentative final monograph on OTC anticaries drug products published in the **Federal Register** on September 30, 1985 (50 FR 39854). Instead, the agency held an open public meeting on September 26 and 27, 1983, regarding unresolved technical issues concerning the LTP's and reopened the administrative record to include the proceedings of the public meeting and to allow comments on matters raised at the meeting. In the second segment of the tentative final monograph for OTC anticaries drug products published in the **Federal Register** of June 15, 1988 (53 FR 22430), the agency considered information generated at the public meeting and in comments and stated that the requirement of lengthy clinical trials to demonstrate anticaries effectiveness of fluoride dentifrices is no longer warranted. Having determined that demonstration of the availability of the fluoride ion in the formulation and satisfaction of the biological testing requirements are the most important testing criteria for predicting the effectiveness of a fluoride dentifrice, the agency stated that appropriate laboratory testing is adequate to assure the effectiveness of fluoride dentifrices containing Category I ingredients. The agency proposed that fluoride dentifrices meet or exceed the soluble fluoride ion level specified for each particular fluoride ingredient listed in the monograph and meet the test requirements of any two of the biological tests recommended by the Dental Panel in its report (53 FR 22435). However, the agency has not evaluated the comments received to date on this proposal.

The agency believes that a dentifrice product containing an ingredient included in the anticaries monograph, i.e., sodium fluoride, sodium monofluorophosphate, or stannous fluoride, that satisfies the requirements of the LTP's has demonstrated anticaries effectiveness. Therefore, the agency has tentatively determined that the LTP's could be used to demonstrate the anticaries effectiveness of the fluoride in any combination dentifrice containing 5 percent potassium nitrate and a Category I fluoride ingredient. The agency is not currently aware of any chemical evidence predictive of an interaction between potassium nitrate and any Category I fluoride ingredient that would alter the bioavailability or effectiveness of either ingredient. In addition, based upon the available evidence, the agency also believes that the combination of 5 percent potassium nitrate and a Category I fluoride ingredient does not decrease the safety of either of the individual active ingredients. Such a combination would provide rational concurrent therapy for a significant target population when used under adequate directions for use and warnings against unsafe use. Therefore, an acceptable dentifrice containing 5 percent potassium nitrate and any Category I fluoride ingredient in combination would need to meet the requirements of the final monographs for OTC anticaries drug products and for OTC relief of oral discomfort drug products.

The agency is therefore proposing to include the combination of 5 percent potassium nitrate and any Category I fluoride ingredient labeled for the relief of hypersensitive teeth and for the prevention of dental caries as Category I in this amendment to the tentative final monograph for OTC oral health care drug products.

The agency notes that no OTC drug advisory review panel considered this combination. In accordance with the agency's Compliance Policy Guide 7132b.16 (which describes the agency's enforcement policy regarding the marketing of OTC combination drug products not reviewed by an OTC drug advisory review panel) (Ref. 10), this specific combination may not be marketed until the Commissioner states by notice in the **Federal Register** that the combination has been tentatively determined to be generally recognized as safe and effective and that OTC marketing of the combination will be permitted under specified conditions. Before marketing may begin, the comment period must have ended and another **Federal Register** notice must have been published setting forth the agency's determination concerning marketing before publication of the final rule. The comment period for this document is 120 days. However, the agency is requesting comments and objections regarding the combination of potassium nitrate and fluoride in a dentifrice drug product in a shorter period of 60 days so that the marketing status of such a combination drug product can be determined in an expeditious manner. Any such marketing that might be allowed, pending issuance of the final monograph, is subject to the risk that the Commissioner may adopt a different position in the final monograph that could require relabeling, recall, or other regulatory action.

The agency's detailed comments and evaluation of the data are on file in the Dockets Management Branch (Ref. 11).

References

(1) Comment No. C00009, Docket No. 80N–0228, Dockets Management Branch.

(2) Comment No. C00017, Docket No. 80N–0228, Dockets Management Branch.

(3) "The Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, 1976, p. 992.

(4) Silverman, G., "Desensitizing Dentifrice Study," draft of unpublished paper, coded LET004, Docket No. 80N–0228, Dockets Management Branch.

(5) Comment No. SUP003, Docket No. 80N–0228, Dockets Management Branch.

(6) Comment No. SUP004, Docket No. 80N–0228, Dockets Management Branch.

(7) Comment No. SUP002, Docket No. 80N–0228, Dockets Management Branch.

(8) Letter with attachments from Block Drug Co., Inc., to W.E. Gilbertson, FDA, coded LET005, Docket No. 80N–0228, Dockets Management Branch.

(9) Comment No. SUP, Docket No. 80N–0228, Dockets Management Branch.

(10) "OTC Drugs—General Provisions and Administrative Procedures for Marketing Combination Products," Food and Drug Administration Compliance Policy Guidelines, 7132b.16, OTC Volume 13BTFM.

(11) Letter from W.E. Gilbertson, FDA, to S. Most, Block Drug Company, Inc., coded LET0010, Docket No. 80N–0228, Dockets Management Branch.

48. Referring to the table summarizing the Dental Panel's categorization of active ingredients (47 FR 22712 at 22725), where the combination of sodium fluoride, strontium chloride, and edetate disodium is listed as a Category II tooth desensitizer, one comment suggested that sodium fluoride and strontium chloride be deleted from this item in this table. The comment stated that edetate disodium is the Category II ingredient and that the combination becomes Category II because of the use of edetate disodium.

The Panel reviewed a combination drug product containing 0.44 percent sodium fluoride, 10 percent strontium chloride, and the chelating agent edetate disodium (Ref. 1), and stated that the purpose of the edetate disodium in this drug product was to maintain the ingredients sodium flouride and strontium chloride in solution by chelating the strontium and preventing the formation of insoluble strontium chloride (47 FR 22750). [In reviewing the data submitted to the Panel (Ref. 1), the agency has determined that the Panel's report erroneously stated strontium chloride at page 22750, and that it should have stated strontium fluoride.] The Panel listed edetate disodium as an inactive ingredient (47 FR 22715) and did not review this ingredient as a single active ingredient. The Panel listed both sodium fluoride and strontium chloride as active ingredients (47 FR 22715), reviewed each of these ingredients as tooth desensitizers (47 FR 22751), and placed both ingredients in Category III. The Panel also placed combinations of two tooth desensitizers in Category III (47 FR 22722).

Because the presence of the inactive ingredient edetate disodium is crucial to maintain the integrity of the combination drug product containing sodium fluoride and strontium chloride, the agency considers edetate disodium a pharmaceutical necessity in this product and concludes that it was appropriate for the Panel to review this product as a separate specific combination. The agency also agrees with the Panel's Category II determination that this specific combination drug product is unsafe for OTC use because the 0.44 percent sodium fluoride concentration represents a safety risk without proven benefit as a tooth desensitizer (the Panel had recommended 0.22 percent sodium fluoride dentifrice as safe for daily use as an anticaries agent (45 FR 20666 at 20682)) and because the chelating properties of the inactive ingredient edetate disodium may cause decalcification of teeth (47 FR 22750). The agency believes that the Panel's intent to place sodium fluoride and strontium chloride as single ingredients in Cagetory III, to place the combination of 0.44 sodium fluoride and 10 percent strontium chloride containing edetate disodium in Category II, and to place combinations of two tooth desensitizers in Category III is clearly stated in the Panel's report and that modification of the Panel's summary table is unnecessary.

Reference

(1) OTC Volume 080010.

F. Comments on Testing Guidelines

49. Two comments requested that the Dental Panel's "Data Required for Evaluation" guidelines (47 FR 22712 at 22756) be reconsidered. The comments felt that some of the protocol requirements were inappropriate, unrealistic, unachievable, obsolete, or in variance with widely accepted methodology. Specific changes were suggested.

The agency has not addressed specific testing guidelines in this document. In revising the OTC drug review procedures relating to Category III, published in the **Federal Register** of September 29, 1981 (46 FR 47730), the agency advised that tentative final and final monographs will not include recommended testing guidelines for conditions that industry wishes to upgrade to monograph status. Instead, the agency will meet with industry representatives at their request to discuss testing protocols. Therefore, the specific changes suggested by the comments are not being addressed in this document. The revised procedures also state the time in which test data must be submitted for consideration in developing the final monograph. (See also part II. paragraph A.2. below.)

50. Several comments objected to seven aspects of the Dental Panel's recommended testing guidelines for reclassifying agents for the relief of toothache in Category I as follows:

(1) The criteria for the selection of patients, specifically the limitation of patient selection to only those with severe pain or only those between the ages of 20 and 50 years; the comments stated that patients of any age should be allowed to participate in the study.

(2) The requirement of a positive control in the testing guidelines; the comments stated that the only Category I ingredient that could be used as a positive control is eugenol, an aromatic, and that use of this ingredient as a positive control is impractical and would not allow adequate blinding of a study.

(3) The use of a sequential analysis design for the testing of agents for the relief of toothache; the comments stated that such a design is impractical because it requires the pairing of patients to receive two different treatments within as short a period of time as possible, not to exceed 1 day. Because patients with toothaches are difficult to obtain, the comments argued that, in many instances, less than two patients with toothache will be seen in a clinic during 1 day.

(4) The method of data analysis; one comment contended that the data collected in a study should be analyzed by standard statistical methodology rather than the statistical methodology used in sequential analysis because, in studying a toothache relief drug product, the investigator cannot normally use the same individual for two different products.

(5) The blinding technique; one comment stated that the Panel's recommendation that, as a blinding technique, eugenol be placed on the tongue of all patients when this ingredient is used as a control in testing would serve no useful purpose and would only confuse the patients.

(6) The Panel's recommendation that the relief of pain last "at least 20 minutes" before the treatment is considered effective; the comments stated that shorter periods of relief from pain are significant and should be considered adequate to demonstrate effectiveness.

(7) The Panel's recommendation that pain be measured as "tolerable" or "intolerable;" one comment stated that it has been standard practice in testing to use pain scales with more than two points of pain discrimination which reliably measure pain reduction. The comment contended that the use of a reliable pain scale would obviate the need to follow the Panel's recommendations to pair patients with the same pain intensity over a short time interval.

Several comments also objected to four aspects of the Panel's recommended testing guidelines for upgrading a Category III tooth desensitizer to Category I as follows:

(1) The Panel's criteria for selecting patients, specifically that each of the three studies should include persons with the same type of sensitivity and that at least one of the three studies must be on persons with Type I sensitivity, defined as hypersensitivity due to periodontal surgery. The comments urged deletion of the requirement that a minimum of 6 weeks pass following periodontal surgery before patients who underwent such surgery are admitted as subjects in a study; also, the comments requested that the selection of patients be made on the presence of subjective pain of dentinal hypersensitivity and on the basis of sound professional judgment. One comment was not aware of any data that suggest that the condition of dentinal hypersensitivity differs depending on its cause (e.g., cervical erosion, abrasion, gingival recession, periodontal surgery) and urged the agency to confine the focus of testing to the condition of dentinal hypersensitivity and not to its causes. The comments objected to the Panel's recommendation that persons selected for test and placebo trials should be of the same sex and be reasonably similar in age, in number of sensitive teeth, and in the mean sensitivity score (47 FR 22712 at 22756). The comments argued that adding sex and age pairing requirements and pairing subjects with teeth having near-identical hypersensitivities unduly compound the problem of timely completion of clinical investigations utilizing large numbers of subjects. The comment contended that hypersensitivity does not appear to be correlated with either patient age or sex.

(2) The requirement of a paired sequential study design (47 FR 22756). The comments were opposed to a paired sequential design for these studies and suggested that sex, age, and sensitivity equivalence for test and placebo trials be specified for groups of patients in study designs other than paired sequential analysis. The comments recommended that persons selected for test and placebo trials should be reasonably similar in the mean sensitivity score so far as is practical.

(3) The Panel's recommendation that teeth which may be included in the study be limited to incisors and premolars in both arches as well as recommendations concerning how many teeth should be examined during each patient evaluation. One comment recommended deleting the requirement that all teeth be examined each time after the initial examination establishes which teeth are sensitive and which are not and urged that only the hypersensitive teeth should be evaluated on subsequent examinations. Also, the comment felt that molars should be allowed to be included in the study if the investigator is able to identify one or more of them as hypersensitive teeth.

(4) The Panel's recommendation that in studies involving tooth desensitizers both the test and placebo materials must be indistinguishable regarding taste, consistency, and appearance (47 FR 22756). The comments believed that the requirement for the placebo to be "indistinguishable" from the active ingredient is unreasonable and suggested terminology used in the tentative final monograph for OTC antiperspirant drug products (47 FR 36492 at 36500). The comments recommended the use of the terms "as similar as possible" to replace "indistinguishable" and the addition of the phrase "as judged by sensory evaluation procedures" to the guidelines.

Comments on the testing guidelines for reclassifying agents for the relief of toothache and for reclassifying tooth desensitizer objected to the Panel's recommendation that three investigators at three separate institutions, preferably academic institutions, should perform studies required to upgrade a Category III ingredient to Category I (47 FR 22756). Two comments believed this requirement is unnecessary because one multiclinical, double-blind study or two separate studies are sufficient to prove efficacy. One comment recommended that the requirement for the number of studies should be consistent with FDA's traditional rule that two well-controlled clinical studies are adequate for demonstrations of efficacy. Two comments believed that "the limitation to an academic setting" was unduly restrictive and should be deleted. The comments felt that flexibility should be allowed for the use of clinics or private practices which can mobilize adequate numbers of patients and demonstrate clinical experience suitable for these studies.

The comments concluded that certain of the testing guideline requirements are inappropriate and unachievable, that others are not realistic or representative of the present state of the art, and that the goal of demonstrating effectiveness can be properly realized by other clinically acceptable protocols. The comments requested that other acceptable procedures should be allowed.

The agency has not addressed specific testing guidelines in this document. In revising the OTC drug review procedures relating to Category III, published in the Federal Register of September 29, 1981 (46 FR 47730), the agency advised that tentative final and final monographs will not include recommended testing guidelines for conditions that industry wishes to upgrade to monograph status. Instead, the agency will meet with industry representatives at their request to discuss testing protocols and the number of studies needed to upgrade Category III conditions to Category I. The revised procedures also state the time in which test data must be submitted for consideration in developing the final monograph. (See also Part II. paragraph A.2. below.) Thus, under the current agency approach, acceptable procedures other than those recommended by the Dental Panel may be allowed.

51. Two comments objected to the Dental Panel's recommendation that a cross-over design be used for studies to demonstrate the effectiveness of an agent for the relief of toothache (47 FR 22712 at 22735) for the following reasons: (1) It would be difficult or impossible to utilize the same patient for a second drug treatment if the first drug treatment relieved the patient's toothache; and (2) ethically, the patient's toothache should be professionally treated as soon as possible. The comments requested that the agency delete this requirement for testing agents for the relief of toothache.

The Panel's recommended testing guidelines are not being included in this proposal. (See comments 49 and 50 above.) The Panel recommended that a sequential analysis study design be used to demonstrate the effectiveness of agents for the relief of toothache. The agency believes that the comments may have misinterpreted the Panel's recommendation. A sequential analysis design does not involve multiple test treatments of the same patient as is required by a cross-over study design. In a sequential analysis design, patients are paired randomly over a time interval that is as short as possible. Each patient of the pair receives only one test treatment. One patient receives one type of treatment and the second patient receives the other type of treatment. The results obtained from treating each of the patients in the pair are then used as the unit of comparison for the two different treatments. Successive pairs of patients are sequentially analyzed until statistically significant differences between the two treatments are achieved. The agency concludes that the Panel's recommended testing guidelines for agents for the relief of toothache would not require a cross-over testing design.

52. Regarding the Dental Panel's recommended testing guidelines for agents for the relief of toothache (47 FR 22712 at 22736), one comment stated that the mode of application of toothache relief drugs should not be specified because the method of application will depend on the ingredient and/or formulation. Another comment stated that the testing procedures should allow for the use of other dosage forms as appropriate. The comment further stated that because a consumer cannot always be expected to find his or her tooth cavity, it is more practical to apply the ingredient to the total tooth surface; therefore, clinical studies should be designed to support the efficacy of agents for the relief of toothache for use in and around the tooth.

In the revision of the OTC drug review procedures relating to Category III, published in the Federal Register of September 29, 1981 (46 FR 47730) and clarified April 1, 1983 (48 FR 14050), the agency advised that, regarding testing procedures, tentative final and final monographs will not include recommended testing guidelines for conditions that industry wishes to upgrade to monograph status. Instead, the agency will meet with industry representatives at their request to discuss testing protocols. (See also Part II. paragraph A.2. below.) The Panel did provide for testing a gel dosage form in its testing guidelines (47 FR 22736), but the agency recognizes that the Panel's recommended testing procedures do not include all possible methods of application and dosage formulations. The agency will consider the use of any appropriate testing procedure even though it may differ from that recommended by the Panel. The Panel's testing criteria are considered to be recommendations to the agency; however, test designs that are used in studies submitted in support of the safety and effectiveness of Category III conditions are evaluated on their own merits rather than on how well they meet the Panel's requirements. Thus, when Category III ingredients are tested for safety and/or effectiveness and subsequently upgraded to Category I, the agency will propose directions for use that are consistent with the manner of application used in the testing procedures. If clinical studies demonstrate the safety and efficacy of agents for the relief of toothache for use in and around the tooth, directions for such use will also be included in the monograph.

II. The Agency's Tentative Conclusions and Adoption of the Dental 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 Dental Panel, as well as other data and information available at this time, and has made some changes in the categorization of relief of oral discomfort active ingredients recommended by the Panel. As a convenience to the reader, the following list is included as a summary of the categorization of relief of oral discomfort active ingredients recommended by the Panel and the proposed categorization by the agency.

Active ingredients	Panel	Agency
1. *Agents for the relief of toothache:*[1]		
Benzocaine	III	III
Benzyl alcohol	III	III
Butacaine sulfate	III	III
Capsicum (as a counterirritant).	II	II
Capsicum (for use in an open tooth cavity).	II	II
Cresol	III	III
Creosote	III	III
Eugenol (85 to 87 percent).	I	III
Eugenol (1 to 84 percent).	III	III
Menthol	II	II
Methyl salicylate	II	II
Phenol preparations (phenol and/or phenolate sodium).	III	III
Thymol preparations (thymol and thymol iodide).	III	III
2. *Oral mucosal analgesics (Topical anesthetics):*		
Benzocaine	I	I
Benzyl alcohol	III	I
Butacaine sulfate	I	I
Camphor	II	II
Chlorophyllin (water-soluble)	Not reviewed	III
Cresol	III	III
Methyl salicylate	II	II
Phenol preparations (phenol and/or phenolate sodium).	I	I
Thymol preparations (thymol and thymol iodide).	III	III
3. *Oral mucosal protectants:*		
Benzoin preparations (benzoin tincture and compound benzoin tincture).	I	I
Myrrh, fluidextract	III	III
4. *Tooth desensitizers:*		
Citric acid and sodium citrate in poloxamer 407 (Pluronic F-127 gel).	III	III
Fluoride preparations (sodium fluoride, sodium monofluorophosphate, and stannous fluoride).	III	III
Formaldehyde solution.	III	III
Potassium nitrate	III	I
Sodium fluoride (0.44 percent), strontium chloride, and edetate disodium (in combination).	II	II
Strontium chloride	III	III

[1] The Panel recommended that beeswax should not be included as an inactive ingredient in products intended for use in an open tooth cavity, and the agency concurs.

2. Testing of Category II and Category III conditions

The Panel recommended testing guidelines for agents for the relief of toothache (47 FR 22712 at 22735) and for tooth desensitizers (47 FR 22712 at 22756). The agency's position regarding the Panel's testing guidelines is discussed in comments 49, 50, and 51 above. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any relief of oral discomfort 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) and clarified April 1, 1983 (48 FR 14050). That policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Changes

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

1. The Dental Panel was charged to review and evaluate dental and dental care drug products including agents for oral mucosal injury and agents for the relief of oral discomfort. Oral mucosal injury drug products are OTC preparations intended to relieve oral soft tissue injury by cleansing or promoting the healing of minor oral wounds or irritations (48 FR 33984 at 33984). Agents for the relief of oral discomfort are OTC preparations to treat minor trauma or irritations of a transient nature to the gums or teeth (47 FR 22712 at 22717). The Oral Cavity Panel was charged to evaluate ingredients in OTC preparations intended for use for the temporary relief of symptoms due to minor irritations, inflammations, and other lesions of the mucous membranes of the oral cavity (47 FR 22760 at 22765). Because of the overlap between the rulemaking on OTC oral mucosal injury drug products and the rulemaking on OTC oral health care drug products, the agency incorporated that part of the oral mucosal injury rulemaking that includes oral wound cleansers into the first segment of the tentative final monograph for OTC oral health care drug products published in the Federal Register of January 27, 1988 (53 FR 2436). Likewise, because the ingredients reviewed as relief of oral discomfort agents and the ingredients reviewed as oral health care drug products are indicated for similar therapeutic purposes in the same area (i.e., the oral cavity), in this document, the agency is merging the advance notice of proposed rulemaking for OTC relief of oral discomfort drug products into the tentative final monograph for OTC oral health care drug products (proposed as 21 CFR part 356). The intent of the combined rulemaking is to identify those ingredients that are generally recognized as safe and effective in temporarily relieving the symptoms associated with minor oral wounds or other irritations of the mouth, gums, or teeth. Combining these two rulemakings into one will result in more consistent labeling on the OTC drug products intended for topical use in the oral cavity and in less confusion for the manufacturers of these drug products and for the consumer.

2. The agency is not including § 354.1 "Scope" of the Dental Panel's recommended monograph for relief of oral discomfort drug products in this proposal because the proposed "Scope" (§ 356.1) of the tentative final monograph for OTC oral health care drug products adequately covers all oral health care drug products including relief of oral discomfort drug products.

3. So that the definition of an oral health care drug will include agents for relief of oral discomfort, the agency is proposing to amend § 356.3(a) of the tentative final monograph for OTC oral health care drug products by adding the words "gums," and "teeth," and the phrase "minor irritations of the gums" to read as follows: "A drug product applied topically for the proper care of the oral cavity, including the temporary relief of symptoms of the gums, teeth, mouth, and throat, for example, minor irritation of the gums, occasional mouth soreness, or minor sore throat."

The agency is also adding a definition for the term "dentifrice" in § 356.3(h) of the definition section of this proposal.

In this proposal, the agency is incorporating the definitions found in § 354.3 of the Dental Panel's recommended monograph for OTC relief of oral discomfort drug products into § 356.3 of the amended tentative final monograph for OTC oral health care drug products. However, the agency is not including the definitions for an "agent for the relief of oral discomfort" or for an "oral mucosal analgesic" found in § 354.3(a) and § 354.3(c), respectively, of the Dental Panel's recommended monograph for relief of oral discomfort drug products. The definition for an "oral health care drug" in § 356.3(a) has been revised to include agents for the

relief of oral discomfort. (See part II. paragraph B.3. above.) Oral mucosal analgesic ingredients are being included in this amendment as anesthetic/analgesic ingredients, and the definition for an "anesthetic/analgesic" in § 356.3(c) of this amendment adequately defines this therapeutic group. Individual definitions are renumbered accordingly.

4. Although the Dental Panel classified 85 to 87 percent eugenol in Category I as an agent for the relief of toothache, the agency has determined that the data are inadequate to demonstrate effectiveness of this ingredient and reclassified the ingredient in Category III for this use. (See comment 7 above.)

5. In this proposal, the agency is not including the agents for the relief of toothache that were recommended by the Dental Panel in § 354.10 of its monograph. Section 356.10 of this proposed monograph is reserved for agents for the relief of toothache should any be classified in Category I in the future.

6. The agency is including oral mucosal analgesics, § 354.12 of the Dental Panel's recommended monograph, in the therapeutic category of OTC oral health care anesthetic/analgesics in § 356.12 of this proposal. Some of the same ingredients (i.e., benzocaine, benzyl alcohol, and phenol) were reviewed as oral mucosal analgesics by the Dental Panel and as anesthetic/analgesics by the Oral Cavity Panel. Oral mucosal analgesics and anesthetic/analgesics are intended for the temporary relief of pain caused by minor irritations or injuries of the oral mucosa. Therefore, the agency believes that these ingredients should be considered to be one therapeutic category. In this proposal, to eliminate duplication and overlap, the agency is proposing to combine the indications, warnings, and directions recommended in § 354.55 for oral mucosal analgesics by the Dental Panel with the indications, warnings, and directions proposed by the agency for anesthetic/analgesics in § 356.55 of the first segment of the tentative final monograph for OTC oral health care drug products. The combined indications, warnings and directions for anesthetic/analgesic active ingredients are found in § 356.52 of this proposal. Additionally, the term "oral mucosal analgesic" is replaced by the term "anesthetic/analgesic" in this proposal.

7. The Dental Panel classified benzyl alcohol in Category III as an oral mucosal analgesic (47 FR 22712 at 22743 to 22744). The Oral Cavity Panel classified benzyl alcohol in Category I as an anesthetic/analgesic it its report (47 FR 22760 at 22809 to 22810), and the agency agreed with the Category I classification in the first segment of the tentative final monograph for OTC oral health care drug products (53 FR 2436). Therefore, in this proposal, the agency is including benzyl alcohol as a Category I anesthetic/analgesic in § 356.12(b).

8. Although butacaine sulfate was not reviewed by the Oral Cavity Panel, the Dental Panel classified it as a Category I oral mucosal analgesic, § 354.12(b). The agency agrees with the Dental Panel's Category I classification and is, therefore, including butacaine sulfate in this proposal in 356.12(e) as an anesthetic/analgesic.

9. The agency is including oral mucosal protectants, § 354.14 of the Dental Panel's proposed monograph, in § 356.20 of this proposal.

10. The agency is including 5 percent potassium nitrate as a Category I tooth desensitizer in § 356.22 of this amendment. (See comment 8 above.)

11. The section containing package size limitations, § 354.18 of the Dental Panel's recommended monograph, is being revised and is included in this amendment in § 356.24. The agency is not including the package size limitations for butacaine sulfate that were recommended by the Dental Panel in § 354.18(a) of its report. Additionally, the agency is revising the directions for use for butacaine sulfate by deleting any reference to single-use packaging. (See comment 35 above.)

12. The Dental Panel classified several combination drug products in Category I and included them in § 354.20 of its proposed monograph at § 354.20. The agency is deferring consideration of recommended § 354.20(b), (c), and (d) to the antimicrobial segment of the rulemaking for OTC oral health care drug products because these recommended combinations all contain antimicrobial ingredients. The agency is proposing to add the Dental Panel's remaining Category I combinations in 354.20 (a) and (e) to the combinations proposed by the agency in § 356.20 of the first segment of the tentative final monograph for OTC oral health care drug products and to include the combinations in this amendment in § 356.26.

13. Because oral mucosal protectants are not indicated for use in sore throat, the agency concludes that when anesthetic/analgesic ingredients are combined with oral mucosal protectants, the indication for anesthetic/analgesics in § 356.52(b)(1), "For the temporary relief of occasional minor irritation, pain, sore mouth, and sore throat," should not be used. The agency also notes that the indication in § 356.52(b)(7), "For products containing * * * when used in denture adhesive products * * *," is not applicable to combination products containing anesthetic/analgesics and oral mucosal protectants because the Panel stated in its report that the use of an oral mucosal protectant in a denture adhesive is irrational (47 FR 22712 at 22722). Therefore, the agency is proposing to include in § 356.66, "Labeling of combination drug products," the following: "For permitted combinations [of oral mucosal protectants and anesthetic/analgesics] identified in § 356.26(c). Any or all of the indications in § 356.52(b)(2), (b)(3), (b)(4), (b)(5), and (b)(6) should be used."

14. The agency has reviewed data and information submitted in support of the safety and effectiveness of a dentifrice containing fluoride (sodium monofluorophosphate) and potassium nitrate for the claims of prevention of cavities and tooth desensitization and has determined that the data are sufficient to demonstrate the effectiveness of this combination. Furthermore, the agency has determined that any Category I fluoride may be used in combination with potassium nitrate as long as the product demonstrates anticaries effectiveness. Therefore, in this proposal, the agency is proposing a Category I classification for the combination of any Category I fluoride ingredient and potassium nitrate used for the prevention of cavities and tooth desensitization. (See comment 47 above.)

15. The warning "Children under 12 years of age should be supervised in the use of this product" in §§ 354.50(c)(1)(vi), 354.55(c)(2) and (c)(4)(i), 354.60(c)(5), and 354.65(c)(3) of the Dental Panel's recommended monograph is not included in the warnings sections of this proposal because the statement appears in the directions for use for all products formulated as mouthwashes (oral rinses). (See comments 27 and 31 above.)

16. The agency is not including in this proposal the warning "Do not swallow" that was recommended by the Dental Panel in §§ 354.50(c)(1)(iv), 354.55(c)(1)(iii), 354.60(c)(3), and 354.65(c)(2). However, for anesthetic/analgesics formulated as mouthwashes (oral rinses), the agency is including the wording "* * * and then spit out" in the directions in §§ 356.52(d)(1)(i), (d)(2)(i), (d)(4)(i), (d)(5)(i), (d)(6)(i), (d)(7)(i)(a) and (d)(7)(i)(b), and (d)(8)(i) of this proposal. (See comment 28 above.)

17. The labeling for agents for the relief of toothache recommended by the Dental Panel in § 354.50 is not being included in this proposal. Section 356.50 in this proposal is reserved for the labeling of agents for the relief of toothache in the event that any ingredients are classified in Category I in the future.

18. The agency is not including in this proposal the Dental Panel's recommended statement of identity for oral mucosal analgesics in § 354.55(a). Oral mucosal analgesics are included as part of the therapeutic category identified as anesthetic/analgesics in § 356.52 (see Part II, paragraph B.5. above), and the statement of identify proposed by the agency in § 356.52(a) is sufficient.

19. The agency is proposing to revise the indications recommended by the Dental Panel in § 354.55(b)(1)(i) and (b)(1)(iii) and § 354.55(b)(3) by using the phrase "mouth and gums" instead of "soft tissues," "soft tissue of the mouth," or "oral tissues." The agency is including the revised indications in § 356.52(b)(3), (b)(5), and (b)(7) of this proposal. (See comment 24 above.)

20. Because canker sores do not require professional diagnosis before self-treatment, the agency is not including in this proposal the indication recommended by the Dental Panel in § 354.55(b)(1)(iv). The indication proposed in § 356.55(b)(2) of the first segment of the tentative final monograph for OTC oral health care drug products is being included in this amendment in § 356.52(b)(2). (See comment 23 above.)

21. The warnings recommended for oral mucosal analgesics by the Dental Panel in § 354.55(c)(1)(i) and (c)(1)(ii) are not being included in this proposal. The agency believes that the intent of those warnings is fulfilled by the warnings proposed for anesthetic/analgesics by the agency in § 356.55(c)(1) and (c)(2) of the first segment of the tentative final monograph for OTC oral health care drug products and is proposing those warnings for anesthetic/analgesic ingredients in § 356.52(c)(1) and (c)(2).

22. The agency is not including in this proposal the warnings recommended specifically for butacaine sulfate by the Dental Panel in § 354.55(c)(4) because the information in these warnings is included in the revised directions for use of butacaine sulfate in § 356.52(d)(3) of this proposal. (See comment 35 above.)

23. The directions for use of benzocaine proposed by the agency in § 356.55(d)(1) and (d)(2) of the first segment of the tentative final monograph for OTC oral health care drug products are being included in this proposal in § 356.52(d)(1)(i) and (d)(1)(ii) as directions for use of benzocaine. The directions recommended for benzocaine by the Dental Panel in § 354.55(d)(1) have been slightly revised by the agency and are being included in this proposal as the directions in § 356.52(d)(1)(iii) for using benzocaine in a teething preparation.

24. The agency is revising the directions recommended by the Dental Panel for butacaine sulfate in § 354.55(d)(2) to eliminate the reference to package size limitations. The agency is including the revised directions in § 356.52(d)(3) of this proposal. (See comment 35 above.)

25. The agency is proposing that the minimum effective concentration of phenol for use as an oral health care anesthetic/analgesic be 0.5 percent rather than 0.25 percent as recommended by the Dental Panel and is including the minimum effective concentration of 0.5 percent in § 356.52(d)(7) of this proposal. (See comment 4 above.)

26. As a result of combining oral mucosal analgesics and oral health care anesthetic/analgesics, the agency is not including the directions for use of phenol as an oral mucosal analgesic recommended by the Dental Panel in § 354.55(d) (3) and (d)(4). The directions proposed for use of phenol as an anesthetic/analgesic by the agency in the first segment of the tentative final monograph for OTC oral health care drug products in § 356.55(d)(6)(i) (a) and (b) and § 356.55(d)(6)(ii) are being proposed in § 356.52(d)(7)(i) and (d)(7)(ii). (See comment 36 above.)

27. The agency is proposing to limit the concentration of phenol in teething preparations to 0.5 percent phenol. Additionally, the agency is proposing to revise the direction it proposed in § 356.55(d)(6) of the first segment of the tentative final monograph for OTC oral health care drug products by adding directions for the use of teething preparations and including those directions in § 356.52(d)(7)(iii) of this proposal. (See comments 4 and 36 above.)

28. The agency is including in §§ 356.52(d)(1)(iv), (d)(3)(ii), and (d)(7)(iv) of this proposal the directions for the use of benzocaine, butacaine, and phenol in dental adhesives that were recommended by the Dental Panel in § 354.55(d)(5).

29. The agency is including in § 356.60 of this proposal the labeling recommended by the Dental Panel for oral mucosal protectants in § 354.60.

30. The agency is proposing to revise the indication recommended by the Dental Panel for oral mucosal protectants in § 354.60(b)(4) "For protecting recurring canker sores when the condition has been previously diagnosed by a dentist" by deleting the phrase "when the condition has been previously diagnosed by a dentist." The agency has determined that canker sores do not require professional diagnosis before self-treatment. (See comment 23 above and part II. paragraph B.21. above.) The revised indication is included in § 356.60(b)(4) of this proposal.

31. The agency has determined that the wording of the warning proposed in the first segment of the tentative final monograph for OTC oral health care drug products in § 356.70(c) for debriding agents/oral wound cleansers is also appropriate for oral mucosal protectants. Therefore, the agency is proposing to combine §§ 354.60(c)(1) and (c)(2) of the Dental Panel's recommended monograph into the following revised warning for oral mucosal protectants (included in this amendment in § 356.60(c)(1)): "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."

32. The agency is revising the labeling recommended for tooth desensitizers by the Dental Panel in § 354.65 and is including the revised labeling in § 356.62 of this proposal.

33. The agency is proposing that the statement of identity for tooth desensitizer drug products recommended by the Dental Panel in § 354.65(a) be revised to provide a choice of dosage forms and a choice between the words "sensitive" and "hypersensitive." (See comment 18 above). The revised statement of identity is included in § 256.62(a) of this proposal.

34. In order to clarify and shorten the language of the monograph the agency has revised the indication recommended by the Dental Panel for tooth desensitizers in § 354.65(b) as follows: "Helps reduce painful sensitivity of the teeth to cold, heat, acids, sweets, or contact." The revised indication is included in § 356.62(b)(1) of this proposal.

35. Because the desensitizing effect of potassium nitrate has been demonstrated to be cumulative, the agency is proposing in this amendment that the following additional indication for tooth desensitizers be included in § 356.62(b)(2): "Builds increasing protection against painful sensitivity of

the teeth to cold, heat, acids, sweets, or contact." (See comment 26 above.)

36. The agency is combining and simplifying the warnings recommended for tooth desensitizers by the Dental Panel in § 354.65(c)(1), (c)(4), and (c)(5) into one warning "Sensitive teeth may indicate a serious problem that may need prompt care by a dentist. See your dentist if the problem persists or worsens. Do not use this product longer than 4 weeks unless recommended by a dentist or doctor." The agency is proposing to include the revised warning in § 356.62(c) of this proposal. (See comment 30 above.)

37. Because the agency does not consider fever, irritation, and infection to be related to dental hypersensitivity, the warning recommended for tooth desensitizers by the Dental Panel in § 354.65(c)(6) is not being included in this proposal. Additionally, the agency is not including the warning recommended by the Dental Panel in § 354.65(c)(7), "Do not exceed recommended dosage," in this amendment. (See comment 31 above.)

38. The agency has revised the directions for use for tooth desensitizers recommended by the Dental Panel in § 354.65(d) and is proposing to include these revised directions for use in § 356.62(d) of this proposal. (See comment 38 above.)

39. The agency is proposing new § 356.66, "Labeling of Combination Drug Products" in which labeling specific to combination drug products containing oral health care ingredients is described.

40. The agency is proposing to include professional labeling for products containing dyclonine hydrochloride in § 356.80(b). The agency is also amending the professional labeling proposed in § 356.80(a) of the first segment of the tentative final monograph for OTC health care drug products to include "Vincent's infection." (See comment 39 above.)

41. 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." That option is proposed in § 356.48(a).

42. Combining the rulemaking for relief of oral discomfort drug products with the rulemaking for oral health care drug products resulted in the redesignation of many section and paragraph numbers. As a convenience to the reader, the following chart is included to show how all of the section and paragraph numbers have been redesignated.

REDESIGNATED SECTION AND PARAGRAPH NUMBERS OF THE TENTATIVE FINAL MONOGRAPH FOR ORAL HEALTH CARE DRUG PRODUCTS AMENDED BY ADDING THE INGREDIENTS AND LABELING FROM THE RULEMAKING FOR RELIEF OF ORAL DISCOMFORT DRUG PRODUCTS

Paragraph number in this amended TFM for oral health care drug products	Paragraph number in the TFM for oral health care drug products (53 FR 2436)	Paragraph number in the ANPR for relief of oral discomfort drug products (47 FR 22712)
356.3(a)	356.3(a)	
356.3(b)		354.3(a)
356.3(c)	356.3(b)	354.3(b)
		354.3(c)
356.3(d)	356.3(c)	
356.3(e)	356.3(d)	
356.3(f)	356.3(e)	
356.3(g)	356.3(f)	
356.3(h)	356.3(g)	
356.3(i)	356.3(h)	
356.3(j)		354.3(d)
356.3(K)		354.3(e)
356.10 (reserved).		354.10
356.12(a)	356.10(a)	354.12(a)
356.12(b)	356.10(b)	
356.12(c)		354.12(b)
356.12(d)	356.10(c)	
356.12(e)	356.10(d)	
356.12(f)	356.10(e)	
356.12(g)	356.10-(f)	354.12(c)
356.12(h)	356.10(g)	
356.14	356.14	
356.16	356.16	
356.18	356.18	
356.20(a)		354.14(a)
356.20(b)		354.14(b)
356.22 (reserved).		354.16
		354.18(a)
356.24		354.18(b)
356.26(a)	356.20(a)	
356.26(b)	356.20(b)	
356.26(c)		354.20(a)
		354.20(b)
		354.20(c)
		354.20(d)
356.26(d)		354.20(e)
356.26(e)	356.20(c)	
356.26(f)	356.20(d)	
356.26(g)	356.20(e)	
356.26(h)		
356.48(a)	356.50(a)	
356.48(b)	356.50(b)	
356.50 (reserved).		354.50
		354.55(a)
356.52(a)	356.55(a)	
356.52(b)(1)	356.55(b)(1)	
356.52(b)(2)	356.55(b)(2)	
354.55(b)(1)(iv)		
356.52(b)(3)		354.55(b)(1)(i)
356.52(b)(4)		
354.55(b)(1)(ii)		
356.52(b)(5)		
354.55(b)(1)(iii)		
356.52(b)(6)		354.55(b)(2)
356.52(b)(7)		354.55(b)(3)

REDESIGNATED SECTION AND PARAGRAPH NUMBERS OF THE TENTATIVE FINAL MONOGRAPH FOR ORAL HEALTH CARE DRUG PRODUCTS AMENDED BY ADDING THE INGREDIENTS AND LABELING FROM THE RULEMAKING FOR RELIEF OF ORAL DISCOMFORT DRUG PRODUCTS—Continued

Paragraph number in this amended TFM for oral health care drug products	Paragraph number in the TFM for oral health care drug products (53 FR 2436)	Paragraph number in the ANPR for relief of oral discomfort drug products (47 FR 22712)
356.52(c)(1)	356.55(c)(1)	
356.52(c)(2)	356.55(c)(2)	
		354.55(c)(1)(i)
		354.55(c)(1)(ii)
		354.55(c)(1)(iii)
356.52(c)(3)		354.55(c)(1)(iv)
		354.55(c)(2)
356.52(c)(4)		354.55(c)(3)
		354.55(c)(4)
356.52(c)(5)		354.55(c)(5)
356.52(c)(6)		354.55(c)(6)
356.52(d)(1)(i)	356.55(d)(1)(i)	354.55(d)(1)
356.52(d)(1)(ii)	356.55(d)(1)(ii)	
356.52(d)(1)(iii)		
356.52(d)(2)(i)	356.55(d)(2)(i)	
356.52(d)(2)(ii)	356.55(d)(2)(ii)	
356.52(d)(3)		354.55(d)(2)
356.52(d)(4)	356.55(d)(3)	
356.52(d)(5)	356.55(d)(4)	
356.52(d)(6)	356.55(d)(5)	
356.52(d)(7)(i)(a)	356.55(d)(6)(i)(a)	
356.52(d)(7)(i)(b)	356.55(d)(6)(i)(b)	354.55(d)(4)
356.52(d)(7)(ii)	356.55(d)(6)(ii)	
356.52(d)(7)(iii)		354.55(d)(3)
356.52(d)(7)(iv)		354.55(d)(5)
356.52(d)(8)	356.55(d)(7)	
356.54	356.65	
356.56	356.70	
356.58	356.75	
356.60(a)		354.60(a)
356.60(b)		354.60(b)
356.60(c)(1)		354.60(c)(1)
356.60(c)(1)		354.60(c)(2)
		354.60(c)(3)
356.60(c)(2)		354.60(c)(4)
		354.60(c)(5)
356.60(d)		354.60(d)
356.62(a)		354.65(a)
356.62(b)(1)		354.65(b)
356.62(b)(2)		
356.62(c)		354.65(c)(1)
		354.65(c)(2)
		354.65(c)(3)
356.62(c)		354.65(c)(4)
356.62(c)		354.65(c)(5)
		354.65(c)(6)
		354.65(c)(7)
356.62(d)		354.65(d)
356.66	356.78	
356.80(a)	356.80(a)	
356.80(b)		
356.80(c)	356.80(b)	

The agency is also designating proposed subpart D of the monograph as subpart C and is placing the labeling sections under subpart C.

43. For an active ingredient to be included in an OTC drug final monograph, it is necessary to have publicly available sufficient chemical information that can be used by all

manufacturers to determine that the ingredient is appropriate for use in their products. Most of the active ingredients that the Dental Panel and the Oral Cavity Panel classified as Category I are standardized and characterized for quality and purity and are included in official compendia. Alum, benzocaine, benzyl alcohol, carbamide peroxide, compound benzoin tincture, dyclonine hydrochloride, gelatin, glycerin, hydrogen peroxide, menthol, pectin, phenol, salicyl alcohol, sodium bicarbonate, and zinc chloride are included as articles in the current United States Pharmacopeia (U.S.P.) or National Formulary (Ref. 1). Although benzoin tincture was included as an article in U.S.P. XV (Ref. 2), it is not included in the current U.S.P. The remaining ingredients (i.e., butacaine sulfate, elm bark, hexylresorcinol, potassium nitrate, and sodium perborate monohydrate) are not adequately characterized.

The agency believes that it would be appropriate for interested parties to develop with the United States Pharmacopeial Convention appropriate standards for the quality and purity of the oral health care ingredients that are not already included in official compendia. In this tentative final monograph, butacaine sulfate, elm bark, hexylresorcinol, potassium nitrate, and sodium perborate monohydrate are proposed in Category I. However, should interested parties fail to provide necessary information so that appropriate standards may be established, these ingredients will not be included in the final monograph. The same standards should also be developed for any Category II or III ingredients for which data are submitted for inclusion in the final monograph.

References

(1) "United States Pharmacopeia XXII—National Formulary XVII," United States Pharmacopeial Convention, Inc., Rockville, MD, 1989, pp. 41, 147, 150, 223 to 224, 485, 611, 663, 821, 1021, 1061, 1236, 1252, 1462, 1906, and 1932.

(2) "United States Pharmacopeia XV," United States Pharmacopeial Convention, Inc., Washington, p. 91, 1955.

The agency is proposing to remove the existing warning and caution statement recommended in § 369.20 for "toothache preparations." That statement reads "For temporary use only until a dentist can be consulted." If ingredients for the relief of toothache are included in the final monograph, the existing statement in § 369.20 will be superseded by the requirements of the final monograph on OTC oral health care drug products (part 356, subpart C). If ingredients for the relief of toothache are not included in the final monograph, products containing these ingredients will need a new drug application for marketing, and there will be no need for the existing statement to appear in § 369.20.

III. Recent Developments

A. Additional Warning(s) for Products Indicated for Relief of Sore Throat

In March 1990, the agency became aware of four reports from the United Kingdom (U.K.) of life threatening pharyngeal spasm that were related to a phenol-containing OTC oral spray used for the symptomatic relief of sore throat (Ref. 1). All cases occurred when people who may have had epiglottitis used the anesthetic/analgesic oral spray. One person died, with the cause of death listed as acute epiglottitis. The only difference in the formulation between the OTC drug product used in the U.K. and a similar product marketed in the United States (U.S.) is that the drug product used in the U.K. contains 0.0145 percent tartrazine as a coloring agent, and the drug product marketed in the U.S. has not contained tartrazine since 1980. The manufacturer of the product informed the agency that the British Committee on Safety of Medicines (CSM) was reconsidering the future marketing of the phenol-containing OTC drug product (Ref. 2).

Subsequently, the CSM permitted continued marketing of the phenol-containing OTC oral spray so long as certain labeling changes were made in both consumer and professional labeling (Ref. 3). The revised labeling states that (1) the product is not for use in children under 12 unless recommended by a doctor; (2) the product should not be used and a doctor consulted if there is a difficulty in breathing, if breathing is noisy, or if there is a severe difficulty in swallowing; and (3) the product should not be used without consulting a doctor if sore throat is severe, has lasted for more than 2 days, or is accompanied by high fever, headache, nausea, or vomiting.

The agency requested information from the company on any serious adverse drug experience reports that it had received from consumers in the U.S., regarding either anaphylactic-like reactions or swelling of the throat or larynx area leading to difficulty in breathing related to the use of the phenol-containing OTC oral health care drug product. The company conducted a review of its data base for the years 1963 to 1990, found a total of 18 reports, and submitted these reports to the agency (Refs. 4 and 5). The reports indicated that adverse reactions occurred both with and without tartrazine in the product. The company also provided the agency with U.S. drug experience reports, specifically anaphylactic-like reactions or swelling of the throat or larynx area resulting in difficulty in breathing, for its OTC drug products indicated for sore throat that contain anesthetic/analgesic ingredients other than phenol (i.e., mentol and benzocaine) (Ref. 5).

The agency contacted manufacturers of the major brands of OTC oral health care drug products containing Category I anesthetic/analgesic ingredients (i.e., benzocaine, benzyl alcohol, dyclonine hydrochloride, hexylresorcinol, menthol, phenol, and salicyl alcohol) (Ref. 6). In addition, the agency contacted the manufacturer of a major brand of an OTC oral health care drug product containing tartrazine (Ref. 6). FDA requested these manufacturers to provide any reports received regarding airway obstruction or anaphylactic-type reactions associated with these products.

The agency has analyzed the information received along with information already in its spontaneous reporting system. Duplicative reports, i.e., industry reports identical with FDA reports, were excluded. A case was included in this analysis only if there was documentation of swelling of the throat, larynx, or epiglottis and/or respiratory difficulty. Reports in which it was noted that the product became lodged in the throat resulting in mechanical obstruction of the airway were not included. The agency has documented 4 cases involving benzocaine, 3 cases involving benzyl alcohol, 38 cases involving dyclonine hydrochloride, 3 cases involving hexylresorcinol, 3 cases involving menthol, 24 cases involving phenol, and 0 cases involving salicyl alcohol. In some cases, only one anesthetic/analgesic ingredient was involved; in others, more than one anesthetic/analgesic ingredient was involved. In addition, the agency has documented nine cases involving tartrazine in combination with a Category III antimicrobial ingredient (i.e., cetylpyridinium chloride). In three of these cases, the product also contained benzyl alcohol. In two of the cases, the product also contained benzocaine (Ref. 6).

The manufacturer of the phenol-containing OTC oral spray discussed above recently informed FDA (Ref. 7) that it intends to enhance the warning statement currently proposed for anesthetic/analgesic ingredients in the tentative final monograph for OTC oral

health care drug products (53 FR 2436 at 2458) on all dosage forms of its OTC oral health care drug products containing any anesthetic/analgesic ingredient and indicated for the relief of sore throat. The manufacturer included a synopsis and evaluation of adverse experience reports involving OTC oral health care anesthetic/analgesic drug products and a review of the characteristics of epiglottitis.

The manufacturer stated that the most prevalent symptoms of epiglottitis are sore throat (often severe), dysphagia (difficulty in swallowing), fever, and dyspnea (difficulty in breathing). It noted that two of the four symptoms (i.e., severe sore throat and fever) are already addressed in the warning proposed by the agency in the OTC oral health care tentative final monograph (53 FR 2436 at 2458), as follows: "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 * * *." The manufacturer noted that this warning does not refer to dysphagia or dyspnea. With regard to dysphagia, the manufacturer stated that preliminary research indicates that there is considerable consumer confusion with respect to difficulty in swallowing. Typically, consumers equate the discomfort or pain of swallowing that accompanies even a minor sore throat with difficulty in swallowing. Patients with epiglottitis, however, frequently experience dysfunction of the epiglottis that does not allow them to swallow normally. The manufacturer stated that consultations with otolaryngologists indicated that when consumers do experience true difficulty in swallowing, as is exhibited by an inability to swallow their own saliva (as can occur with epiglottitis), they are extremely unlikely to use an OTC oral anesthetic/analgesic. The manufacturer, therefore, concluded that the addition of "difficulty in swallowing" to the warning statement for OTC oral health care anesthetic/analgesic drug products would not convey a clear or meaningful message to consumers, but rather it would likely prevent the appropriate use of such products.

However, the manufacturer maintained that dyspnea or difficulty in breathing is well understood by the consumer. Therefore, although specialists in otolaryngology have advised that adult epiglottitis patients experiencing such symptoms are unlikely to use any OTC sore throat product, the manufacturer believes that the addition of this symptom to the warning statement adds a further measure of assurance that OTC oral health care anesthetic/analgesic drug products will not be used in inappropriate situations.

The manufacturer concluded that the currently proposed warning statement for OTC oral health care drug products (see above) could be clarified by making a few simple changes, thereby providing further assurance that such OTC drug products will not be misused. The manufacturer proposed a revised warning as follows:

> If sore throat is severe, or is accompanied by difficulty in breathing, or persists for more than 2 days, do not use and consult a doctor promptly. If sore throat is accompanied by 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 doctor or dentist promptly.

The manufacturer further stated that it intends to phase in this enhanced warning statement on all of its oral anesthetic/analgesic drug products as current labeling inventory is exhausted (Ref. 7).

The agency believes that the number of adverse event reports involving either anaphylactic-like reactions or swelling of the throat or larynx area leading to difficulty in breathing and related to the use of oral health care drug products indicated for relief of sore throat symptoms demonstrates the need for labeling to highlight this potential problem. Epiglottitis is a severe, rapidly progressive infection of the epiglottis and surrounding tissues that may be quickly fatal because of sudden respiratory obstruction by the inflamed structures (Ref. 8). Its incidence is highest in children 2 to 5 years of age, but it may occur at any age. Sore throat, hoarseness and, usually, high fever develop abruptly in a previously healthy child. The patient should be hospitalized immediately if epiglottitis is suspected (Ref. 7). The agency believes that the labeling on all OTC oral health care products indicated for use in relieving the symptoms of sore throat should alert consumers to the possibility that they may need immediate medical attention if certain symptoms are present. However, at this time, the agency is not including such language in this tentative final monograph, but instead is requesting comment on how best to convey such information to consumers.

There are several questions that need to be addressed. The warning statement proposed in §§ 356.52(c)(1), 356.54(c), and 356.58(c)(1) of this amendment for ingredients indicated for use in relieving the symptoms of sore throat (i.e., anesthetic/analgesics, astringents, and demulcents) is as follows: "If sore throat is severe, persists for more than 2 days, is accompanied by or followed by fever, headache, rash, swelling, nausea, or vomiting, consult a doctor promptly * * *." The agency seeks comment on whether "difficulty in breathing," "noisy breathing," or "difficulty in swallowing" should be added to this warning. If so, how should the warning be worded to best alert consumers to these potential problems?

The agency notes that the warning statement required by the CSM for the phenol-containing oral spray discussed above states that the product is "Not to be used by children under 12 years of age unless recommended by a doctor." The directions for use being proposed in this amendment indicate that children under 12 years of age should be supervised in the use of liquid dosage forms. Solid dosage forms may be used by adults and children 2 years of age and older without supervision, except for phenol-containing products, which may only be used by adults and children 6 years of age and older. Because the incidence of epiglottitis is highest in children aged 2 to 5 years (Ref. 8), the agency seeks comment on whether the use of products indicated for the relief of sore throat should now also be limited to adults and children over a certain age e.g., 6 or 12 years.

Finally, the agency would like comment on whether any revised warning statements should apply only to products containing anesthetic/analgesic ingredients, or should such warning statements apply to any OTC drug product that is indicated for treating a sore throat. The agency believes that any revised warning statement should apply to any OTC oral health care drug product used to treat a sore throat.

Based on comments received, if necessary, the agency will propose revised labeling for OTC oral health care drug products indicated for the relief of soar throat in an amendment to this tentative final monograph.

References

(1) Letter from M. D. Young, The Procter & Gamble Co., to M. D. Tyson, FDA, dated March 2, 1990, in OTC Volume 13BTFM.

(2) Minutes of Meeting between Richardson-Vicks, Inc., The Procter & Gamble Co., and FDA, dated March 5, 1990, in OTC Volume 13BTFM.

(3) Letter from R. A. Stolt, Richardson-Vicks, Inc., to D. Barash, FDA, dated June 15, 1990, in OTC Volume 13BTFM.

(4) Letter from R. A. Stolt, Richardson-Vicks, Inc., to D. Barash, FDA, dated March 9, 1990, in OTC Volume 13BTFM.

(5) Letter from R. A. Stolt, Richardson-Vicks, Inc., to D. Barash, FDA, dated August 2, 1990, in OTC Volume 13BTFM.

(6) Summary of Adverse Reaction Reports Regarding Airway Obstruction/Anaphylactic-type Reactions Associated with Oral Health Care Anesthetic/Analgesic Products, Food and Drug Administration, March 11, 1991, in OTC Volume 13BTFM.

(7) Letter from R. A. Stolt, Richardson-Vicks, Inc., to W. E. Gilbertson, FDA, dated February 19, 1991, in OTC Volume 13BTFM.

(8) "Acute Epiglottitis," in "The Merck Manual of Diagnosis and Therapy," ed. by R. Berkow and A. J. Fletcher, Merck, Sharp & Dohme Research Laboratories, Rahway, NJ, 1987, pp. 2020 and 2021.

B. Artificial Saliva Drug Products

The agency has recently become aware of several currently marketed artificial saliva drug products that are indicated for use as mouth moisteners and oral lubricants for individuals with permanent or temporary salivary gland disfunction (i.e., xerostomia). These preparations are designed to mimic natural saliva both chemically and physically (Ref. 1). They usually consist of an aqueous solution containing a thickening agent, a humectant, and electrolytes usually found in saliva. Their consistency approaches that of normal saliva, and their electrolyte levels are adjusted to approximate those of natural saliva (Ref. 2). They do not stimulate saliva production and, thus, must be considered as replacement therapy, not as a cure for xerostomia (Ref. 1).

Xerostomia, a condition in which saliva production is severely limited or completely arrested, has a various etiology and may be either temporary or permanent depending upon the cause (Ref. 2). Temporary xerostomia is often a side effect caused by the administration of various classes of drugs (e.g., antihistamines, decongestants, diuretics, and antihypertensives). The condition disappears when drug therapy ceases. Permanent xerostomia may be caused by exposure of the salivary glands to radiation therapy for the treatment of malignant neoplasms of the head or neck, or it may be a symptom of an autoimmune disease such as Sjogren's syndrome. The adverse effects of chronic xerostomia include stomatitis, burning tongue, reduced denture wearing time, difficulty in swallowing and speaking, disturbed sleep patterns, rampant caries, and periodontal disease (Refs. 1 and 2).

The agency believes that artificial saliva products could be potentially useful for individuals suffering from either temporary or permanent xerostomia. However, no submissions were made to the Panel or the agency regarding these products, nor is the agency aware of any specific data that would establish general recognition of safety and effectiveness. Therefore, the agency invites specific data and information regarding the use of artificial saliva drug products. After review and evaluation of the data submitted, the agency will consider artificial saliva drug products for inclusion in the final monograph for OTC oral health care drug products.

References

(1) Baker, K. A., "Oral Health Products," in "Handbook of Nonprescription Drugs," 9th Ed., American Pharmaceutical Association, Washington, 1990, pp. 667, 668, and 679.

(2) "Accepted Dental Therapeutics," 39th Ed., American Dental Association, Chicago, 1982, pp. 52, 53, 54, and 324.

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 relief of oral discomfort drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act (Pub. L. 96-354). That assessment included a discretionary regulatory flexibility analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC relief of oral discomfort 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 relief of oral discomfort drug products. No comments on economic impacts were received. Any comments on the agency's initial determination of the economic consequences of this proposed rulemaking should be submitted by January 22, 1992. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

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

Interested persons may, on or before January 22, 1992, submit to the Dockets Management Branch written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. Written comments, objections, or requests for oral hearing on the combination of potassium nitrate and an anticaries active ingredient, identified in § 356.26(h), by November 25, 1991. 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 January 22, 1992. 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 September 24, 1992, 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 November 24, 1992. 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. 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 November 24, 1992. 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 356

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

21 CFR Part 369

Labeling, Medical devices, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 356 (as proposed in the Federal Register of May 25, 1982 (47 FR 22712) and the Federal Register of January 27, 1988 (53 FR 2436)) and 21 CFR part 369 be amended as follows:

1. Part 356 is revised to read as follows:

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

Subpart A—General Provisions

Sec.

Subpart B—Active Ingredients

Subpart C—Labeling

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

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 of this chapter.

(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 gums, teeth, mouth, and throat, for example, minor irritation of the gums, occasional mouth soreness, or minor sore throat.

(b) *Agent for the relief of toothache.* An ingredient used for the temporary relief of pain arising as a result of an open tooth cavity.

(c) *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).

(d) *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.

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

(f) *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.

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

(h) *Dentifrice.* A substance used with a toothbrush to clean the accessible surfaces of the teeth. It is an abrasive-containing dosage form for delivering an active ingredient to the teeth.

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

(j) *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.

(k) *Oral mucosal protectant.* An ingredient which is a pharmacologically inert substance which forms an adherent, continuous, flexible, or semirigid coating when applied to the oral mucous membranes. The coating protects the irritated area from further irritation due to the activity of oral structures.

(l) *Tooth desensitizer.* An ingredient which acts on the dentin to block perception of those stimuli which are usually not perceived by subjects with normal teeth but which are perceived by patients with dental hypersensitivity.

Subpart B—Active Ingredients

§ 356.10 Agents for the relief of toothache.

§ 356.12 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 § 356.52(d).

(a) Benzocaine.
(b) Benzyl alcohol.
(c) Butacaine sulfate.
(d) Dyclonine hydrochloride.
(e) Hexylresorcinol.
(f) Menthol.
(g) Phenol preparations (phenol and/or phenolate sodium).
(h) 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 § 356.54(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 § 356.56(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 § 356.58(d):

(a) Elm bark.

(b) Gelatin.

(c) Glycerin.

(d) Pectin.

§ 356.20 Oral mucosal protectants.

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 § 356.60(d).

(a) Compound benzoin tincture, U.S.P. XIX.

(b) Benzoin tincture, U.S.P. XV.

§ 356.22 Tooth desensitizers.

The active ingredient of the product consists of potassium nitrate when used within the dosage limits and in the dosage form established in § 356.62(d).

§ 356.24 Package size limitations.

Products containing benzoin preparations identified in § 356.20 should be packaged in well-closed containers in a quantity of 30 milliliters or less.

§ 356.26 Permitted combinations of active ingredients.

(a) Any single anesthetic/analgesic active ingredient identified in § 356.12 may be combined with any single astringent active ingredient identified in § 356.14.

(b) Any single anesthetic/analgesic active ingredient identified in § 356.12 may be combined with any single demulcent active ingredient identified in § 356.18.

(c) Any single oral mucosal protectant active ingredient identified in § 356.20 may be combined with any single anesthetic/analgesic active ingredient identified in § 356.12.

(d) Any single anesthetic/analgesic active ingredient identified in § 356.12 may be combined with any generally recognized safe and effective denture adhesive.

(e) Benzocaine identified in § 356.12(a) may be combined with menthol identified in § 356.12 (f).

(f) Benzocaine identified in § 356.12(a) may be combined with phenol preparations identified in § 356.12 (g).

(g) Oral health care and cough-cold combinations. See § 341.40 of this chapter.

(h) Potassium nitrate identified in § 356.22 may be combined with any single anticaries active ingredient identified in § 355.10(a) of this chapter.

Subpart C—Labeling

§ 356.48 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) Indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable. 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) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (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.

§ 356.50 Labeling of drug products for the relief of toothache.

§ 356.52 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," any of the phrases listed below:

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

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

(3) "For the temporary relief of pain due to minor irritation or injury of the mouth and gums."

(4) "For the temporary relief of pain due to minor dental procedures."

(5) "For the temporary relief of pain due to minor irritation of the mouth and gums caused by dentures or orthodontic appliances."

(6) *For products containing benzocaine identified in § 356.12(a) or phenol identified in § 356.12(g) when used as anesthetic/analgesics for teething pain.* "For the temporary relief of sore gums due to teething in infants and children 4 months of age and older."

(7) *For products containing any ingredient identified in § 356.12 when used in denture adhesive products.* "For the temporary relief of pain or discomfort of the mouth and gums due to dentures."

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

(1) *For all products containing any ingredient identified in § 356.12 labeled with only the indication in § 356.52(b)(1) or with the indication in § 356.52(b)(1) plus any of the indications in § 356.52(b)(2), (b)(3), (b)(4), (b)(5), (b)(6), or (b)(7).* "If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, swelling, nausea, or vomiting, consult a doctor promptly. If sore mouth symptoms do not improve in 7 days, or if irritation, pain, or redness persists or worsens, see your dentist or doctor promptly."

(2) *For all products containing any ingredient identified in § 356.12 labeled with any of the indications in § 356.52(b)(2), (b)(3), (b)(4), (b)(5), (b)(6), or (b)(7) but not with the indication in § 356.52(b)(1).* "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."

(3) "Do not exceed recommended dosage."

(4) *For all products containing any ingredient identified in § 356.12 (a) and (c).* "Do not use this product if you have a history of allergy to local anesthetics such as procaine, butacaine, benzocaine, or other 'caine' anesthetics."

(5) *For all products labeled with the indication identified in § 356.52(b)(6).* "Fever and nasal congestion are not symptoms of teething and may indicate the presence of infection. If these symptoms persist, consult your doctor."

(6) *For all products containing any ingredient identified in § 356.12 when used in denture adhesive products.* "See your dentist as soon as possible."

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

(1) *For products containing benzocaine identified in § 356.12(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.

(iii) *For products intended to be used as teething preparations, the product is a 5- to 20-percent solution or suspension.* Apply to the affected area not more than four times daily or as directed by a dentist or doctor. For infants under 4 months of age there is no recommended dosage or treatment except under the advice and supervision of a dentist or doctor.

(iv) *For denture adhesive products the product contains 5 to 20 percent benzocaine.* Apply on area of denture that comes in contact with sore gums.

(2) *For products containing benzyl alcohol identified in § 356.12(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 contoining butacaine sulfate identified in § 356.12(c)*—(i) *The product contains 30 milligrams butacaine sulfate per dosage unit.* Adults: Apply (manufacturer should state specific amount of product that contains 30 milligrams butacaine sulfate) to the affected area. Do not apply again for at least 3 hours. Do not use more than three applications in 24 hours unless directed by a dentist or doctor. Children under 12 years of age: Consult a dentist or doctor.

(ii) *For denture adhesive products the product contains 30 milligrams butacaine sulfate per dosage unit.* Apply on area of denture that comes in contact with sore gums.

(4) *For products containing dyclonine hydrochloride identified in § 356.12(d)*—(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.

(5) *For products containing hexylresorcinol identified in § 356.12(e)*—(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 this 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.

(6) *For products containing menthol identified in § 356.12(f)*—(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.

(7) *For products containing phenol preparations identified in § 356.12(g)*—(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.

(iii) *For products intended for use as a teething preparation, the product is an aqueous solution or suspension containing phenol or phenolate sodium equivalent to 0.5 percent phenol.* For infants and children 4 months to under 12 years of age: Apply to the affected area. Use up to 6 times daily or as directed by a dentist or doctor.

(iv) *For denture adhesive products, the product contains phenol or phenolate sodium equivalent to 0.5 to 1.5 percent phenol.* Apply on area of denture that comes in contact with sore gums.

(8) *For products containing salicyl alcohol identified in § 356.12(h)*—(i) *For dosage forms other than solid, the produce 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 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.

§ 356.54 Labeling of astringent 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 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": *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.

§ 356.56 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," any of the phrases listed below: (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) "Assist in the removal of foreign material from minor wounds."

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

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings": *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 product 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 four times daily after meals and at bedtime or as directed by a dentist or doctor. Children under 12 years of age should be supervised in the use of this product. Children under 2 years of age: Consult a dentist or doctor.

(ii) *For use as 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 four times daily after meals and at bedtime or as directed by a dentist or doctor. Children under 12 years of age should be supervised in the use of this product. Children under 2 years of age: Consult a dentist or doctor.

(2) *For products containing hydrogen peroxide identified in § 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 four times daily after meals and at bedtime or as directed by a dentist or doctor. Children under 12 years of age should be supervised in the use of this product. Children under 2 years of age: Consult a dentist or doctor.

(ii) *For use as an oral rinse.* 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 four times daily after meals and at bedtime or as directed by a dentist or doctor. Children under 12 years of age should be supervised in the use of the product. Children under 2 years of age: Consult a dentist or doctor.

(3) *For products containing sodium 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 four 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.

§ 356.58 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 products containing elm bark 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.* 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 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 dentist or 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.

§ 356.60 Labeling of oral mucosal protectant 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 mucosal protectant."

(b) *Indications.* The labeling of the product states, under the heading "Indications," any of the phrases listed below:

(1) "Forms a coating over a wound."

(2) "Protects against further irritation."

(3) "For temporary use to protect wounds caused by minor irritations or injury."

(4) "For protecting recurring canker sores."

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

(1) "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."

(2) "Do not exceed recommended dosage."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions": *For products containing compound benzoin tincture or benzoin tincture identified in § 356.20(a) and (b), the product is compound benzoin tincture, U.S.P. XIX or benzoin tincture, U.S.P. XV.* Adults and children 6 months of age and older: Dry the affected area. Saturate a cotton applicator with medication. Apply the undiluted medication directly to the affected area. Do not use more often than every 2 hours. Children under 6 months of age: Consult a dentist or doctor.

§ 356.62 Labeling of tooth desensitizer drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a (insert dosage form, e.g., "toothpaste" or "dental gel") "for" (select one of the following: "sensitive" or "hypersensitive") "teeth."

(b) *Indications.* The labeling of the product states, under the heading "Indications," any of the phrases listed below:

(1) "Helps reduce painful sensitivity of the teeth to cold, heat, acids, sweets, or contact."

(2) "Builds increasing protection against painful sensitivity of the teeth to cold, heat, acids, sweets, or contact."

(c) *Warnings.* The labeling of the product contains the following warning under the heading "Warnings." "Sensitive teeth may indicate a serious problem that may need prompt care by a dentist. See your dentist if the problem persists or worsens. Do not use this product longer than 4 weeks unless recommended by a dentist or doctor."

(d) *Directions.* The labeling for products containing potassium nitrate identified in § 356.22, as a 5 percent dentifrice, contains the following information under the heading "Directions": Adults and children 12 years of age and older: Apply at least a 1-inch strip of the product onto a soft bristle toothbrush. Brush teeth thoroughly for at least 1 minute twice a day (morning and evening) or as recommended by a dentist or doctor. Make sure to brush all sensitive areas of the teeth. Children under 12 years of age: Consult a dentist or doctor.

§ 356.66 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 over-the-counter (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 in this paragraph. Other truthful and nonmisleading statements, describing only the indications for use that have been established in the applicable OTC drug monographs or listed in this paragraph, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (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 § 356.26(c).* Any or all of the indications in § 356.52(b)(2), (b)(3), (b)(4), (b)(5), and (b)(6) should be used.

(2) *For permitted combinations identified in § 356.26(g).* The indications in § 341.85(b)(4) of this chapter should be used.

(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 in this paragraph.

(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 in this paragraph. When the time intervals or age limitations for administration of the individual ingredients differ, the directions for the combination product:

(1) May not contain any dosage that exceeds those established for any individual ingredient in the applicable OTC drug monograph(s), and

(2) May not provide for use by any age group lower than the highest minimum age limit established for any individual ingredient.

§ 356.80 Professional labeling.

(a) The labeling of products containing oral health care anesthetic/analgesic active ingredients identified in § 356.12 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," "Vincent's infection," or "stomatitis.")

(b) The labeling of products containing dyclonine hydrochloride identified in § 356.12(d) provided to health professionals (but not to the general public) may contain the following indications:

(1) "For the temporary relief of discomfort in patients with an excessive gag reflex when having impressions of the teeth made or during intraoral radiography."

(2) "For use as a preinjection topical anesthetic on the oral mucosa."

(c) The labeling of products containing oral health care 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

2. The authority citation for 21 CFR part 369 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371).

§ 369.20 [Amended]

3. In subpart B, § 369.20 *Drugs; recommended warning and caution statements* is amended by removing the entry for "TOOTHACHE PREPARATIONS."

Dated: July 1, 1991.

David A. Kessler,

Commissioner of Food and Drugs.

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