DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

21 CFR Part 353

[Docket No. 78N-0196]

Oral Mucosal Injury Drug Products for Over-the-Counter Human Use, Establishment of a Monograph; Proposed Rulemaking

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: This proposed rule would establish conditions under which over-the-counter (OTC) oral mucosal injury drug products (drugs which relieve oral soft tissue injury by cleansing or promoting the healing of oral wounds) are generally recognized as safe and effective and not misbranded. The proposed rule, based on the recommendations of the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products, is part of the ongoing review of OTC drug products conducted by the Food and Drug Administration (FDA).

DATES: Comments by January 24, 1980, and reply comments by February 25, 1980.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on April 28, 1978, a report of the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products. Under § 330.10(a)(6) (21 CFR 330.10 (a)(6)), the agency is issuing (1) a proposed regulation containing the monograph recommended by the Panel, which establishes conditions under which OTC oral mucosal injury drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel that they would result in the drugs not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel that the available data are insufficient to classify such conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The report has been prepared independently of FDA, and the agency has not yet fully reviewed the report. The Panel's findings appear in this document as a formal proposal to obtain public comment before the agency reaches any decision on the Panel's recommendations. This document represents the best scientific judgment of the Panel members but does not necessarily reflect the agency's position on any particular matter contained in it.

After FDA has carefully reviewed all comments submitted in response to this proposal, the FDA will issue a tentative final regulation in the **Federal Register** to establish a monograph for OTC oral mucosal injury drug products.

In accordance with § 330.10(a)(2) (21 CFR 330.10(a)(2)), the Panel and FDA have held as confidential all information concerning OTC oral mucosal injury drug products submitted for consideration by the Advisory Review Panel on Dentifrice and Dental Care Drug Products.

All the submitted information will be put on public display at the office of the Hearing Clerk, Food and Drug Administration after November 26, 1979, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD-510) (address above).

Based upon the conclusions and recommendations of the Panel, the agency proposes the following:

1. That the conditions included in the monograph, under which the drug products would be generally recognized as safe and effective and not misbranded (Category I), be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

2. That the conditions excluded from the monograph because they would cause the drug to be not generally recognized as safe and effective or to be misbranded (Category II), be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the **Federal Register,** regardless of whether further testing is undertaken to justify their future use.

The agency advises that the status of Category III conditions after publication of a final order is the subject of the recent decision in *Cutler* v. *Kennedy,* No. 77-0734 (D.D.C. July 16, 1979). In that case, the court held that "* * * the FDA may not lawfully maintain Category III in any form in which drugs with Category III conditions * * * are exempted from enforcement action." (*Cutler, supra.,* Slip Op. at 38). The agency is presently studying the effect of this decision on the OTC drug review procedures. Accordingly, although this document retains the concept of Category III in its original form, the agency's response to the court's decision may result in substantial changes in the regulatory treatment of Category III conditions.

In the **Federal Register** of January 5, 1972 (37 FR 85), the FDA announced a proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels. In the **Federal Register** of May 11, 1972 (37 FR 9464), the agency published the final regulations providing for the OTC drug review under § 330.10 which were made effective immediately. Pursuant to these regulations, the agency issued in the **Federal Register** of January 30, 1973 (38 FR 2781) a request for data and information on all active ingredients utilized in dentifrice and dental care drug products except mouthwashes and oral antiseptics.

The agency appointed the following Panel to review the data and information submitted and to prepare a report pursuant to § 330.10(a)(1) on the safety, effectiveness, and labeling of those products:

Louis P. Gangarosa, D.D.S., Ph.D., Chairman
Joseph J. Aleo, D.D.S., Ph.D. (appointed September 1, 1973)
Howard H. Chauncey, D.M.D., Ph.D. (resigned April 30, 1976)
Valerie Hurst, Ph.D.
Joy B. Plein, Ph.D.
Delos E. Raymond, D.D.S.
Roger H. Scholle, D.D.S., M.S.
Lawrence E. VanKirk, Jr., D.D.S., M.P.H. (appointed June 29, 1976)
Benjamin O. Watkins, D.D.S. (resigned August 1, 1973)

The Panel was first convened on April 24, 1973 in an organizational meeting. Working meetings were held on May 24 and 25, June 21 and 22, August 15 and 16, October 10 and 11, November 29 and 30, 1973; January 17 and 18, February 27 and 28, April 3 and 4, May 9 and 10, June 19 and 20, July 24 and 25, September 19 and 20, October 16 and 17, December 4 and 5, 1974; January 15 and 16, February 26 and 27, April 2 and 3, May 7 and 8, June 24 and 25, August 12, 13, and 14, October 9 and 10, December 3 and 4, 1975;

January 23 and 24, February 24 and 25, March 31 and April 1, May 11 and 12, June 30 and July 1, July 28 and 29, August 25 and 26, October 5 and 6, December 1 and 2, 1976; January 12 and 13, March 9 and 10, April 20 and 21, June 1 and 2, July 13 and 14, August 24 and 25, October 19 and 20, November 30 and December 1, 1977; January 17 and 18, March 11 and 12, April 26, 27, and 28, May 30 and 31, and June 1, and July 11, 12, and 13, 1978.

The minutes of the Panel meetings are on public display in the office of the Hearing Clerk (HFA-305), Food and Drug Administration (address given above).

Five nonvoting liaison members served on the Panel. Judy Jackson, Esq., nominated by the Consumer Federation of America, served as the consumer liaison until April 1974. Mary Plaska, nominated by the American Public Health Association, succeeded Ms. Jackson in May 1974 and served until May 1976. Sandra Zimmerman, nominated by the Consumer Federation of America, succeeded Ms. Plaska in June 1976. Lester D. Apperson, Ph.D., nominated by the Cosmetic, Toiletry, and Fragrance Association, served as an industry liaison. Joseph L. Kanig, Ph.D., nominated by the Proprietary Association, also served as an industry liaison until January 1978.

The following employees of the Food and Drug Administration served: Clarence C. Gilkes, D.D.S. served as Executive Secretary. Michael D. Kennedy served as Panel Administrator until January 1978 followed by Thomas D. DeCillis, R.Ph. Melvin Lessing, M.S., R.Ph. served as Drug Information Analyst until June 1977. George Kerner, M.S. serves as Consumer Safety Officer. Cindy Barkdull served as special assistant from July 1977 to April 1978. Elmer M. Plein, Ph.D. and Gordon H. Schrotenboer, Ph.D. served as consultants to the Panel.

The following individuals were given an opportunity to appear before the Panel to express their views either at their own or at the Panel's request on all issues before the Panel:

John E. Alman, M.A.
Hazen J. Baron, D.D.S., Ph.D.
I. B. Bender, D.D.S.
Malcolm Boone, D.D.S.
R. K. Boutwell, Ph.D.
Herbet Brilliant, D.D.S.
Richard C. Brogle, Ph.D.
Finn Brudevold, D.D.S.
Lewis P. Cancro, Ph.D.
A. Chasens, D.D.S.
Neal W. Chilton, D.D.S.
Stephen A. Cooper, D.M.D., Ph.D.
D. Walter Cohen, D.D.S.
William E. Cooley, Ph.D.
Robert Ellison, D.D.S., M.S.
H. Fogels, D.D.S.
Sol Gershon, Ph.D.
William Gold, Ph.D.
Hans Graf, D.D.S.
F. Healey, Ph.D.
John Hefferren, Ph.D.
L. Kenneth Hiller, Ph.D.
George F. Hoffnagle, Sc.D.
Herschel S. Horowitz, D.D.S., M.P.H.
Marvin Kamisky, Ph.D.
Krishan Kapur, D.M.D., M.Sc.
Kenneth Kasses, Ph.D.
Homer Jamison, D.D.S., Ph.D.
Philip B. Lawson
Edgar Lazo-Wasem, Ph.D.
Donald A. M. MacKay, Ph.D.
John H. Manhold, D.M.D.
Craig R. Means, D.D.S., M.Sc.
Murray Rosenthal, M.S.
Albert L. Russell, D.D.S., M.Ph.
Bernard Schneider, D.D.S.
James H. Stanton
Willard J. Tarbet, D.D.S., Ph.D.
Patrick Toto, D.D.S.
Aaron Trubman, D.D.S.
Paul Vinton, D.D.S.
Carrol S. Weil, M.A.
Elizabeth K. Weisburger, Ph.D.
S. C. Yankell, D.D.S.
K. Yeh, Ph.D.
A. Albert Yurkstas, D.M.D.

No person who so requested was denied an opportunity to appear before the Panel.

The Panel was charged to review submitted data and information for OTC dentifrice and dental care drug products. Because all such agents are not used for the same purpose, it was not possible for the Panel to establish a single standard of requirements for effectiveness of each product. Therefore, in an attempt to simplify categorization of ingredients and labeling claims the Panel placed the dental care drug products into one of the following therapeutic classifications: (1) Agents for oral mucosal injury, (2) agents for the relief of oral discomfort, (3) anticaries agents, (4) dental plaque disclosing agents, and (5) denture aids.

On May 28, 1976, the Medical Device Amendments of 1976 became law. This legislation amends the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.) and provides new authority to assure the safety and effectiveness of medical devices. Several products previously regulated as drugs that were under review by the Panel came within the definition of a medical device under these amendments. The FDA reviewed the products previously regarded as drugs and concluded that the following products in the **Federal Register** of December 16, 1977 (42 FR 63472) fall within the definition of a medical device: Denture cushions, dental adhesives, dental reliners and repair kits, denture cleansers, and plaque-disclosing kits. The Panel wishes to point out that during its deliberations "kits" were not specifically addressed and that the Panel's terminology for dental devices differs from that published in the **Federal Register**. The Panel used the following terminology in evaluating these products: Denture adhesives, denture reliners, denture repair products, denture cleansers, and dental plaque-disclosing agents.

In a notice published in the **Federal Register** of May 2, 1978 (43 FR 18769), FDA announced that it had transferred the responsibility for regulating OTC dental care devices from the agency's Bureau of Drugs to its Bureau of Medical Devices and Diagnostic Products (BMDDP). In addition, the notice announced that the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products had summarized its findings and recommended that the agency transfer that portion of its report concerning products now regulated as medical devices, together with the data and information submitted in response to the January 30, 1973 notice, to BMDDP. A summary of the Panel's conclusions concerning the safety, effectiveness, and labeling of those products is included in the Panel's minutes for the March 11 and 12, 1978 meeting.

The Panel presents its conclusions and recommendations for oral mucosal injury drug products in this document. The Panel's conclusions and recommendations for the relief of oral discomfort drug products and anticaries drug products will be presented in future issues of the **Federal Register**.

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from interested persons, and has considered all pertinent data and information submitted through April 26, 1978, in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel's findings with respect to OTC oral mucosal injury drug products are set out in three categories:

Category I. Conditions under which OTC oral mucosal injury drug products are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC oral mucosal injury drug products are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

I. Submission of Data and Information

Pursuant to the notice published in the **Federal Register** of January 30, 1973 (38

FR 2781) requesting the submission of data and information on OTC drugs containing dentifrice and dental care agents, the following firms made submissions relating to the indicated products that, the Panel has further determined, contain active ingredients or labeling which may be appropriately classified as oral mucosal injury drug products.

A. *Submissions by Firms*

Firms and *Marketed products*

A-Trol Laboratories, Topeka, KA 66604—I.D. Denture Medication.
Carter Products, Cranbury, NJ 08512—Aerodent (Green IV) Dentifrice, Hydrogen Peroxide.
Church & Dwight Co., Inc., Syracuse, NY 13201—Arm and Hammer Baking Soda.
Cooper Laboratories, Inc., Cedar Knolls, NJ 07927—Amosan.
International Pharmaceutical Corp., Warrington, PA 18976—Gly-Oxide Liquid.
McKesson Laboratories, Fairfield, CT 06430—Ora-Fix Medicated Denture Adhesive.
Merrell-National Laboratories, Cincinnati, OH 45215—Cepacol Mouthwash.
Rystan Co., Inc., White Plains, NY 10605—Chloresium Toothpaste, Chloresium Dental Ointment, Chloresium Solution.
Warner-Lambert Co., Morris Plains, NJ 07950—Listerine Antiseptic.
Carter-Wallace, Inc., Cranbury, NJ 08512—Dicalcium Phosphate, Hydrogen Peroxide, Sodium Fluoride.

B. *Labeled Ingredients Contained in Marketed Products Submitted to the Panel*

Alcohol
Allantoin
Benzocaine
Benzoic acid
Boric acid
Carbamide peroxide in anhydrous glycerol
Cetylpyridinium chloride
Eucalyptol
Hydrogen peroxide
Menthol
Methyl salicylate
Phosphate buffers
Sodium bicarbonate
Sodium bitartrate
Sodium perborate monohydrate
Sodium peroxyborate monohydrate (derived from sodium perborate) buffered with sodium bitartrate
Thymol
Thymol iodide
Water-soluble derivatives of chlorophyll "a"

C. *Classification of Ingredients*

1. *Active ingredients (for oral mucosal injury).*

Allantoin
Carbamide peroxide in anhydrous glyceron (carbamide peroxide in anhydrous glycerol)
Chlorophyllins water-soluble (water-soluble derivatives of chlorophyll "a")
Hydrogen peroxide in aqueous solution
Sodium perborate monohydrate (sodium peroxyborate monohydrate)

2. *Inactive ingredients.*

Glycerin
Phosphate buffers
Sodium bitartrate

3. *Ingredients to be discussed by the Panel in subsequent documents issued in the Federal Register either as OTC drugs for the relief of oral discomfort or as anticaries agents.*

Benzocaine (as an oral mucosal analgesic and as a toothache relief agent)
Menthol (as an oral mucosal analgesic)
Methyl salicylate (as an oral mucosal analgesic and as a toothache relief agent)
Sodium bicarbonate (as an anticaries agent)

4. *Ingredients deferred to the Advisory Review Panel on OTC Oral Cavity Drug Products for evaluation for oral antiseptic claims*

Alcohol
Benzoic acid
Boric acid
Cetylpyridinium chloride
Eucalyptol
Menthol
Sodium perborate monohydrate
Thymol
Thymol iodide

D. *Referenced OTC Volumes*

All "OTC Volumes" cited throughout this document include submissions made by interested persons pursuant to the call-for-data notice published in the **Federal Register** of January 30, 1973 (38 FR 2781). All of the submitted information included in these volumes, except for those deletions which are made in accordance with § 330.10(a)(2) (21 CFR 330.10(a)(2)), will be put on public display after November 26, 1979, in the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

II. General Statements and Recommendations

A. *General Comments*

The OTC Dentifrice and Dental Care Agents Panel was charged with the review and the evaluation of safety and effectiveness data on dentifrice and dental care ingredients and combinations thereof, the adequacy of their labeling, and to advise the Commissioner on the promulgation of monographs establishing conditions under which these OTC drug products are generally recognized as safe and effective and not misbranded. The Panel also served as a forum for the exchange of views regarding the prescription or nonprescription status of these various active ingredients and combinations thereof. Panel members were expected to call upon their own expert knowledge and experience in carrying out each element of this charge.

This document contains both general statements and recommendations applicable to the entire class of products reviewed by the Panel as well as specific statements and recommendations applicable to oral mucosal injury drug products.

B. *Definitions*

The following definitions have been adopted by the Panel. These definitions reflect the Panel's intended meaning of terms as specifically used in this document in reference to oral mucosal injury drug products. Some of these definitions also apply to the other drug categories reviewed by the Panel. Some degree of variation with more widely accepted defintions of the same terms may exist.

1. *Buffering agent.* An agent or system which has the ability to resist a change in pH (hydrogen ion concentration), particularly in aqueous solution, upon the addition of an acid, alkali, or upon dilution with a solvent.

2. *Dental care agent.* Any drug or dosage form used to treat or prevent disease of the teeth or soft tissue in the oral cavity.

3. *Dental (dentin) hypersensitivity.* A term which implies that the teeth are much more reactive than normal to sensory stimuli such as heat, cold, sour, sweet, or touch. Hypersensitivity can occur when dentin is exposed to the oral environment as a result of abrasion, erosion, gingival recession, or a defect in the enamel or cementum.

4. *Dentifrice.* In this document a dentifrice is a substance used with a toothbrush to clean the accessible surfaces of the teeth. Dentifrices are ordinarily composed of water, detergent, humectant, binder, and flavoring agents and a finely powdered abrasive as the principal ingredient. In this document, dentifrice is considered to be an abrasive-containing dosage form for delivering therapeutic ingredients.

5. *Dosage.* A quantitative schedule that includes the amount of drug that is ingested or applied at one time (the dose) and the time intervals at which the dose is given; the schedule may include the duration of therapy.

6. *Dosage form.* The pharmaceutical preparation, e.g., solution, suspension, paste, tablet, ointment, in which the drug is administered.

7. *Dose.* The quantity of a drug that is ingested or applied at one time.

8. *Dose-response.* The relationship between the dose of a drug and the magnitude of the effect produced by that dose.

9. *Double-blind study.* A testing procedure in which neither the investigator nor the subject (patient) knows whether an experimental drug or its control has been given.

10. *Gingivitis.* Inflammation occurring in the marginal and/or papillary gingiva as a response to bacterial plaque.

11. *Hypersensitivity.* Literally means "more sensitive than normal." In general health care, the term is almost synonymous with allergy and implies that the person has been exposed to a drug, develops antibodies to it, and then reacts adversely to the drug upon subsequent exposure whereas the normal subject does not (see definition 3 above—Dental (dentin) hypersensitivity).

12. *Minor gum disorders (injury).* Inflammation related to mechanical irritation or minor injury of the gingival tissues. The Panel does not consider gingivitis caused by dental plaque to be a minor gum disorder amenable to self-diagnosis or treatment by OTC preparations.

13. *Mouthwash (oral rinse).* A resolution often containing breath-sweetening, astringent, demulcent, detergent, and/or germicidal agents which is used for freshening and cleansing the mouth, or for gargling. In some instances, such a vehicle may be used to deliver an active drug to the oral mucosa or teeth. The Panel prefers the terms oral rinse and dental rinse according to their respective areas of use (for the oral mucosa or the teeth) rather than mouthwash.

14. *Necrosis.* Refers to circumscribed localized areas of cell or tissue death caused by almost any type of severe injury.

15. *Oral mucosal analgesic (topical anesthetic).* An ingredient used in dental care drug products for surface application in the oral cavity to provide temporary relief of oral discomfort by an analgesic or anesthetic effect.

16. *Oral mucosal injury.* Injury occurring to the soft tissue in the oral cavity.

17. *Oral mucosal injury agent.* An agent which relieves oral soft tissue injury, e.g., by cleansing or promoting the healing of oral wounds (minor oral irritations).

18. *Oral mucosal protectant.* An agent 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.

19. *Oral wound cleanser.* A nonirritating preparation which assists (physically or chemicaly) in the removal of foreign material from small superficial oral wounds and does not delay wound healing.

20. *Oral wound healing agent.* A nonirritating agent which aids in the healing of small superficial oral wounds by means other than cleansing and irrigating, or by serving as a protectant.

21. *Pharmacotherapeutic.* The Panel classified ingredients into various pharmacotherapeutic groups according to the expected therapeutic effect at the intended site of action.

22. *Placebo.* An inactive substance or preparation used in controlled studies to determine the effectiveness of an agent presumed to be active. Generally, a placebo preparation will be identical to the test preparation except that the active or test agent will not be present.

23. *Professional labeling.* Drug directions for the use of a product intended for, and distributed only to, health care professionals.

24. *Prophylactic.* The term "prophylactic" indicates the prevention of disease. In this document, "prophylactic" is synonymous with "preventative."

25. *Sloughing.* A slough is a mass of dead tissue in, or cast out from, living tissue. Sloughing is the formation or separation of dead tissue from living tissue.

26. *Systemic effect.* An effect related to the entire body as contrasted to a local effect, which is an effect on one specific structure. In general, drugs which are absorbed into the blood stream can be assumed to exert systemic effects, although the desired and the observable sites of action may be fairly specific structures or organs.

C. The Dentist and OTC Drugs in Oral Health

The level of sophistication of dental science has accelerated at a remarkable rate in the past two decades. This era has seen the introduction of (1) an air turbine for high-speed tooth cutting, (2) improved methods of pain control, (3) new scientific findings in pulpal and periodontal biology, (4) advances in oral microbiology and plaque control, (5) modern restorative materials including tooth sealants, and (6) expanded research and utilization of paradental personnel. Modern dental practice now stresses total comprehensive dental care including the prevention of disease, multiple restoration at a single appointment, and preservation of natural teeth. Good examples of the new approach in dental care are the current emphasis on prevention of caries by fluorides and the promotion of mechanical plaque-control hygiene programs which are believed to prevent periodontal disease and caries.

In spite of these advances in dentistry, the need for dental care remains high and is thought to be increasing. Among factors responsible for the continuing need and increasing demand for dental care are (1) consumer education and sophistication, (2) availability of funds from increased personal income and from third-party payment plans, (3) requests by labor groups and low socioeconomic groups for more dental, as well as general, health care, and (4) the continuing use of refined diets.

Because of these factors, it is anticipated that the dental profession will be unable to keep up with consumer demand for oral health care. Therefore, an increasing demand for self-medication with OTC drugs will occur. Some OTC drugs may provide preventative care or temporary relief of symptoms of disease and injury.

The Panel is aware that there is a tremendous need for chemical agents to counteract gingivitis and control bacterial plaque. Control of plaque could reduce dental disease. However, it is difficult to achieve adequate control in the majority of the population. Children are not attentive to this need, while handicapped persons may be unable to carry out the plaque-control program which requires diligence and manual skills. Agents with antiplaque and antigingivitis properties should be developed through research by the pharmaceutical industry, by dental schools, and by governmental agencies. For such an agent to become an OTC drug quickly, it should be a drug presently in use in the U.S.A. for another purpose, either as an OTC or a prescription drug. However, it appears that such antiplaque and antigingivitis agents, if they are forthcoming, will be newly developed drugs requiring new drug application (NDA) approval. If after a period of testing they are proven safe and effective, and if they can be labeled for safe and effective nonprescription drug use, they may achieve OTC status.

The Panel wishes to emphasize that currently marketed mouthwashes containing antiseptics do not automatically fulfill the requirements of an agent which has an effect on plaque formation or which prevents gingivitis. The Panel is aware that dental plaque and gingivitis represent two of the leading dental health problems in the country today. For this reason the Panel initiated a discussion of, and search for, agents that could be generally recognized as safe and effective for the control, or prevention, of plaque and of gingivitis.

As a result of this discussion a number of ingredients and rationales for prevention or control of these conditions were submitted.

Present evidence suggests that good oral hygiene is important to the prevention or reduction of inflammatory periodontal disease (Ref. 1). This essentially means the removal of dental bacterial plaque and their products from teeth on a regular basis. The removal or reduction of these offending agents is best accomplished by mechanical means. The effectiveness of a patient's ability to remove offending agents mechanically depends upon the alignment of the teeth, the presence of cavities or calculus, and whether the supporting tissues are well adapted to the teeth.

To supplement mechanical removal of offending agents, a number of chemical agents claiming usefulness for prevention of plaque, calculus, or gingivitis are presently under investigation. The potential value and safety of these agents, which include quaternary ammonium compounds, enzymes, organic fluorides, and various antibiotics have not been conclusively ascertained. The specific antimicrobial compounds for which some success is claimed in clinical studies include several agents. Among them are cetylpyridinium chloride and combinations of cetylpyridinium chloride and domiphen bromide which achieved a 30 to 40 percent reduction in dental plaque (Refs. 2 and 3). Other potentially effective agents include thymol and eucalyptol (Ref. 4), alexidine (Ref. 5), peroxides (Ref. 6), chlorhexidine (Ref. 7), and an investigational compound CC10232 (Ref. 2). A major concern in the use of these agents is their tendency to disrupt the normal microbial ecologic balance of the host (Ref. 8).

After considering these ingredients and the theories and rationale proposed for the effectiveness of drugs used for prevention and control of plaque and gingivitis, the Panel has concluded that such approaches are at present so controversial that there can be no general recognition of the effectiveness of these agents for these indications at this time.

The Panel, therefore, recommends that all claims stating or implying prevention, control, or treatment of plaque or gingivits be placed in Category II and further recommends that antiplaque and antigingivitis agents be investigated and approved through the NDA process.

References

(1) Loe, H., E. Theilade, and S. B. Jensen, "Experimental Gingivitis in Man," *Journal of Periodontology*, 36:177–187, 1965.

(2) Volpe, A. R., et al., "Antimicrobial Control of Bacteria Plaque and Calculus and the Effects of these Agents on Oral Flora," *Journal of Dental Research*, 48:832–841, 1969.

(3) Beiswanger, B. B., O. P. Sturzenberger, and W. Bollmer, "Clinical Effect of an Antibacterial Mouthwash on Dental Plaque and Gingivitis," (Abstract), *Journal of Dental Research, Special Abstract Supplement (International Association for Dental Research)*, p. 146, 1974.

(4) Gomer, R. M., et al., "The Effect of Oral Rinses on the Accumulation of Dental Plaque," *Journal of the American Society for Preventive Dentistry*, 1:6–9, 1972.

(5) Lobene, R. R., and P. M. Soparkar, "The Effect of an Alexidine Mouthwash on Human Plaque and Gingivitis," *Journal of the American Dental Association*, 87:848–851, 1973.

(6) Shipman, B., E. Cohen, and R. S. Kaslick, "The Effect of Urea Peroxide Gel on Plaque Deposits and Gingival Status," *Journal of Periodontology*, 42:283–285, 1971.

(7) Schroeder, H. E., T. M. Marthaler, and H. R. Muhlemann, "Effects of Some Potential Inhibitors on Early Calculus Formation," *Helvetica Odontologica Acta*, 6:6–9, 1962.

(8) Draus, F. W., "The Microbiology of the Oral Cavity and its Systemic Significance," *Dental Clinics of North America*, 2:309, 1958.

D. Labeling for OTC Dental Products

Having reviewed all of the labels of OTC dental preparations submitted, the Panel recommends that labeling include the following:

1. *Labeling.* The Panel reviewed and concurs with the OTC drug regulation labeling (§ 201.61 (21 CFR 201.61)) which states:

(a) The principal display panel of an over-the-counter drug in package form shall bear as one of its principal features a statement of the identity of the commodity.

(b) Such statement of identity shall be in terms of the established name of the drug, if any there be, followed by an accurate statement of the general pharmacological category(ies) of the drug or the principal intended action(s) of the drug. In the case of an over-the-counter drug that is a mixture and that has no established name, this requirement shall be deemed to be satisfied by a prominent and conspicuous statement of the general pharmacological action(s) of the mixture or of its principal intended action(s) in terms that are meaningful to the layman. Such statements shall be placed in direct conjunction with the most prominent display of the proprietary name or designation and shall employ terms descriptive of general pharmacological category(ies) or principal intended action(s); for example, "antacid," "analgesic," "decongestant," "antihistaminic," etc. The indications for use shall be included in the directions for use of the drug, as required by section 502(f)(1) of the act and by the regulations in this part.

(c) The statement of identity shall be presented in bold face type on the principal display panel, shall be in a size reasonably related to the most prominent printed matter on such panel, and shall be in lines generally parallel to the base on which the package rests as it designed to be displayed.

2. *Ingredients.* Dentifrice and dental care agents should contain only active ingredients plus such inactive ingredients as may be necessary for formulation. The label should state the quantity of each active ingredient in appropriate units to be specified later in each section of this document. The Panel encourages the use of metric units.

The Panel strongly recommends that all inactive ingredients be listed on the label in descending order of quantity, since the consumer may need to know, for a variety of reasons, the ingredients in the product. However the product should not imply or claim that its inactive ingredients have a therapeutic benefit.

The Panel recognizes that although full disclosure of flavoring and coloring ingredients is desirable, this may be impractical and confusing because of the large number of ingredients which may be involved. Thus, flavoring and coloring ingredients may be listed in accordance with present regulations for labeling such ingredients in food products.

3. *Indications.* The indications for use of a dentifrice or dental care agent should be simply and clearly stated.

Statements of indications for use should be specific and confined to the conditions for which the product is recommended. Indications should be confined to those that a significant portion of the target population can reasonably self-diagnose. No reference should be made, or implied, regarding the alleviation or relief of symptoms unrelated to the condition accepted as an indication for use of the product.

Thus, a prominent and conspicuous statement must be made of general pharmacotherapeutic action. In addition, the Panel recommends that the label contain a clear indication of the categories of dentifrice or dental care agent and provide the user with a reasonable expectation of the results to be anticipated from use of the product. For example, oral mucosal injury drug products shall be labeled as either an "oral wound cleanser" or an "oral wound healing agent."

4. *Directions for use.* The directions for use should be clear, direct, and provide the user with sufficient information to enable safe and effective use of the product.

The label should include a clear statement of the usually effective minimum and 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. In appropriate instances, the usual directions may be followed by "except under the supervision of a dentist or physician." The Panel will recommend specific directions for use under each drug statement in later sections of this document.

E. Principles Applicable to Combination Products

1. *General combination policy.* In order to clarify the status of combination products in the marketplace, the Panel applied the OTC drug review regulation (§ 330.10(a)(4)) which states:

> (iv) An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

A product may contain two Category I active ingredients that meet the regulatory requirements as well as the criteria adopted by the Panel, together with suitable inactive ingredients, provided that (a) the active ingredients are safe and effective and do not antagonize the therapeutic usefulness of each other, (b) the inactive ingredients are safe and do not interact with, or otherwise inhibit the effectiveness of the active ingredients, (c) there is a significant target population that has the concurrent symtoms and can thus benefit from use of the combination, (d) use of the combination does not decrease the safety due to adverse effects over use of the single ingredient, and (e) the combination contains adequate directions for use and is labeled with adequate warnings against unsafe use.

The Panel recognizes that some OTC dentifrice and dental care agent products contain combinations of ingredients. The Panel found that such combinations contain active ingredients both from the same and from different pharmacotherapeutic classes. The Panel is not convinced that combinations containing two or more oral mucosal injury agents from the same pharmacotherapeutic group would be more effective than the single ingredient alone. Moreover, combining full therapeutic concentrations of two or more ingredients for the relief of oral mucosal injury may incur unwarranted additional risk.

The alternative to combining two ingredients from the same pharmacotherapeutic class at each ingredient's effective dose is to combine subtherapeutic doses of the ingredients, on the theory that such a combination will reduce the risk of side effects or adverse reactions. The Panel prefers full concentrations of single ingredients, because it is not aware of any data to support the use of two ingredients in subtherapeutic doses. Combinations containing ingredients of the same pharmacotherapeutic group at less than the minimum effective concentration for any one of the ingredients are, therefore, classified in Category II.

The Panel recognizes that oral mucosal injury drug products have also been combined with active ingredients from other pharmacotherapeutic groups. The Panel has reviewed and classified combinations of oral mucosal injury active ingredients with active ingredients for the relief of oral discomfort, as discussed below.

The Panel is aware that oral mucosal injury active ingredients have also been combined with oral antiseptic, which are presently under review by the OTC advisory Review Panel on Oral Cavity Drug Products, and with denture adhesives, which are being reviewed by the Bureau of Medical Devices. These combination products were reviewed and classified by this Panel as to their rational for concurrent therapy.

The same general principles apply when an active ingredient from a different pharmacotherapeutic group reviewed by another OTC drug advisory Panel is combined with an active ingredient of a pharmacotherapeutic group reviewed by this Panel. The rationale for such combinations should be evaluated by FDA according to the combination policy set forth in the reports of both panels.

The Panel recognizes the extensive marketing history of many dental preparations. Members of the drug industry presented data to the Panel summarizing their marketing history and consumer complaint information. A number of marketed products are combinations which originated as dentists' private formulas or which has been adapted from formulas appearing in older editions of such compendia as the "Pharmaceutical Recipe Book" or the "National Formulary." The effectiveness of such products may never have been subjected to scientific assessment even though the products have been marketed for many years. Apparent consumer acceptance and testimonial data used by many manufacturers as the sole evidence of effectiveness and safety were not acceptable to the Panel. When claims of effectiveness were supported solely by outdated experimental methodology, this evidence for effectiveness was also considered unacceptable.

Regarding effectiveness, the Panel has applied the OTC drug review regulation (§ 330.10(a)(4)(ii)), which provides that the reports of significant human experience during marketing are appropriate as a source of corroboration for proof of effectiveness. In accordance with these regulations, the Panel took into account the marketing experience of manufacturers as stated in their submissions. Although the Panel found these data helpful, marketing experience did not overrule or substitute for the Panel's other sources of knowledge of safety, effectiveness, and rationale for such combinations. Marketing experience, alone, cannot be regarded as constituting adequate proof of effectiveness, nor should it be the only basis for assessing the rationality and validity of a combination drug product.

2. *Limitation of ingredients in combination products.* The Panel believes that the interests of the consumer are best served by exposing a user of OTC drugs to the fewest ingredients and the lowest dosage that will provide a satisfactory level of effectiveness. Single component OTC drugs are preferable because they afford a lower risk of undesirable side effects and permit more precise treatment of individual symptoms. The Panel recognizes that there may be a rationale for combining active ingredients in certain OTC drugs; however, such combinations must be based on a sound and logical scientific rationale.

The Panel recommends that not more than two dentifrice and dental care agent active ingredients be included in any combination product because the addition of more ingredients would increase the risk to the consumer without increasing the benefit.

3. *Labeling of active ingredients.* The labeling must indicate the name and quantity (concentration) of all active ingredients, and the principle intended action of each ingredient as well as the indication for use of the product. The Panel considers that the labeling for any product that contains an active ingredient for which no claim is made is misleading.

The Panel recommends that the labeling of a combination product containing active ingredients for treatment of two or more concurrent symptoms should emphasize that the consumer use the product only when all such symptoms are present. The

consumer should be adequately informed, through the labeling, of the total therapeutic capabilities of the product.

The Panel recommends that each claimed active ingredient in a combination product must make a statistically significant contribution to the claimed effect or effects of the product.

4. *Criteria for Category I combinations.* The Panel recommends the following general criteria for Category I combination drug products for the treatment of oral mucosal injury.

Two dentifrice and dental care agent 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 from the concurrent symptoms; and the combination is as safe and as effective as each individual active ingredient used alone.

Labeling for the combination product must conform to recommended labeling for each active ingredient, and must specify any additional information such as drug interactions or adverse reactions that occur with the combination product, but not with the individual ingredients used alone. The labeling for a Category I combination product should stress that the product should be used only when both symptoms are present. The consumer needs to be properly informed about the therapeutic capabilities of the product. The product's labeling should not induce the consumer to take a combination drug when a single entity is appropriate and effective.

5. *Category I combination drug products for the treatment of oral mucosal injury.* The Panel recommends that the following combinations be classified as Category I for the treatment of oral mucosal injury.

a. *Combinations of an oral mucosal injury agent with an oral antiseptic.* (**Note.**—the advisability of adding an antiseptic for the stated purpose is under review by the OTC Advisory Review Panel on Oral Cavity Drug products.)

(i) *An oral wound cleanser and an oral antiseptic.* The Panel finds that this combination is rational and should provide additional protection from infection for an oral wound.

(ii) *An oral wound healing agent and an oral antiseptic.* The Panel finds that this combination is rational, and the antiseptic should help prevent infection, thus allowing healing to occur as rapidly as possible. At this time there are no Category I oral wound healing agents, but in the event data are generated to support the movement of an oral wound healing agent into Category I, this combination would be acceptable.

b. *Combinations of an oral mucosal injury agent with a denture adhesive.* (**Note.**—the advisability of adding a denture adhesive for the stated purpose is under review by the Bureau of Medical Devices.)

(i) *An oral wound healing agent and a denture adhesive.* The Panel finds that this combination is rational. There is a target population of persons who wear dentures and develop minor wounds or sores under the denture. This combination should contain a label instructing users that the combination should not be used unless both concurrent symptoms are present.

6. *Criteria for Category II combination products.* The Panel recommends the following criteria for Category II combination drug products for the treatment of oral mucosal injury.

a. A combination is Category II if a Category II active ingredient or Category II labeling is present in the combination product.

b. A combination product containing Category I active ingredients from the same or different pharmacotherapeutic groups is classified as Category II if it includes any ingredient in less than the minimum effective concentration established by the Panel.

c. If a combination contains an active ingredient or other condition that has not been reviewed by this or any other OTC drug advisory review panels, such ingredient or condition is Category II and the resulting combination then becomes Category II.

d. A combination product is classified as Category II if it includes more than two active ingredients from different pharmacotherapeutic groups.

e. A combination product is classified as Category II if it contains active ingredients from more than one pharmacotherapeutic group and there is not a significant target population that has a concurrent need for a drug from each of these groups.

f. A combination is Category II if there is no therapeutic rationale for the combination, even if the individual ingredients are Category I and the combination conforms in all other respects to the criteria for a Category I combination.

g. A combination of two Category I active ingredients from different pharmacotherapeutic groups is Category II if the ingredients cannot be combined because of chemical or physical formulation problems that would result in decreasing the safety or effectiveness of the individual ingredients.

7. *Category II combination drug products for the treatment of oral mucosal injury.* The Panel recommends that the following combinations be classified as Category II for the treatment of oral mucosal injury.

a. *Combinations of two oral mucosal injury agents*—(i) *Oral wound cleanser and an oral wound cleanser.* The Panel finds no rationale for such a combination. The Panel considered whether the combination of short-acting and a long-acting agent would be useful, but such a combination is not on the market. Based on current directions for use of oral wound cleansers (spit out after 1 minute), such a combination does not appear useful.

(ii) *Oral wound cleanser and an oral wound healing agent.* The Panel finds no rationale for such a combination. If an oral wound healing agent is administered in the same dosage form with an oral wound cleanser, the oral wound healing agent will be removed from its site of action when the oral wound cleanser is spit out before it has had an opportunity to exert its intended pharmacotherapeutic effect. In addition, when an oral wound healing agent is used, prolonged contact with the wound area is desired. These two pharmacotherapeutic agents are intended to be used sequentially and not at the same time.

(iii) *Oral wound healing agent and an oral wound healing agent.* The Panel finds no rationale for such a combination. The Panel did not review any data relating to such combinations. There may be a rationale for combining two such agents if each acts by a different mechanism of action but data must be generated to establish that each ingredient makes a contribution to the claimed effect.

b. *Combinations of an oral mucosal injury agent with an agent for the relief of oral discomfort*—(i) *Oral wound cleanser and an oral mucosal protectant.* The Panel finds no rationale for such a combination. An oral mucosal protectant forms a protective film over the area to which it is applied. The use of an oral wound cleanser in the same dosage form with an oral mucosal protectant would result in the cleanser removing the protectant from the affected area, thus making the protectant ineffective.

(ii) *Oral wound cleanser and a toothache relief agent.* The Panel finds no rationale for such a combination. If a toothache relief agent is administered in the same dosage form with an oral wound cleanser, the toothache relief agent will be removed from its site of

action when the oral wound cleanser is spit out and, thus, before it has had an opportunity to exert its intended pharmacotherapeutic effect. These two pharmacotherapeutic agents are intended to be used at different sites in the oral cavity.

(iii) *Oral wound cleanser and an oral mucosal analgesic.* The Panel finds no rationale for such a combination. If an oral mucosal analgesic is administered in the same dosage form with an oral wound cleanser, the oral mucosal analgesic will be removed from its site of action when the oral wound cleanser is spit out. These two pharmacotherapeutic agents are intended to be used sequentially and not at the same time.

(iv) *Oral wound cleanser and a counterirritant.* The Panel finds no rationale for such a combination. By definition, a counterirritant is irritating, and such an agent should not be used when cleansing a wound.

(v) *Oral wound cleanser and a tooth desensitizer.* The Panel finds no rationale for such a combination.

(vi) *Oral wound healing agent and a toothache relief agent.* An oral wound healing agent is intended for use on mucosal tissue, not on tooth pulp. A toothache relief agent is intended for use on irreversibly damaged pulp and should only be used when there is no possibility that the pulp injury is reversible. Hence, an oral wound healing agent would confer no benefit when applied to tissue that has no potential for healing.

(vii) *Oral wound healing agent and a counterirritant.* The Panel finds no rationale for such a combination. By definition, a counterirritant is irritating, and such an agent should not be used on a healing wound.

(viii) *Oral wound healing agent and a tooth desensitizer.* The Panel finds no rationale for such a combination.

(ix) *Peroxide-containing oral wound healing agent and a oral mucosal protectant.* The Panel finds no rationale for such a combination. If an oral mucosal protectant is administered in the same dosage form with a peroxide-containing oral wound healing agent, the bubbling action of the peroxide would remove the protectant from the site of action before it has had an opportunity to exert the intended pharmacotherapeutic effect.

(x) *Peroxide-containing oral wound healing agent and a oral mucosal analgesic.* The Panel finds no rationale for such a combination. If an oral mucosal analgesic is administered in the same dosage form with a peroxide-containing oral mucosal analgesic, the bubbling action of the peroxide would remove the analgesic from the site of action before it has had an opportunity to exert the intended pharmacotherapeutic effect.

c. *Combination of an oral mucosal injury agent with a denture adhesive.* (Note: the advisability of adding a denture adhesive for the stated purpose is under review by the Bureau of Medical Devices.)

(i) *An oral wound cleanser and a denture adhesive.* The Panel finds no rationale for such a combination. The bubbling action of the oral wound cleanser would be antagonistic to the adhesive and might dislodge it.

8. *Criteria for Category III combination products.* The Panel recommends the following criteria for Category III combination drug products for the treatment of oral mucosal injury.

a. 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.

9. *Category III combination drug products for the treatment or oral mucosal injury.* The Panel recommends that the following combinations be classified as Category III for the treatment of oral mucosal injury.

a. *Combinations of an oral mucosal injury agent with certain agents for the relief of oral discomfort*—(i) *nonperoxide-containing oral wound healing agent and a oral mucosal protectant.* These two types of agents may be combined providing testing is performed to establish that the oral mucosal protectant does not interfere with the action of the oral wound healing agent. The protectant will hold the oral wound healing agent in place at the site of the wound and will also protect the wound from further injury and irritation.

(ii) *Nonperoxide-containing oral wound healing agent and a oral mucosal analgesic.* The oral mucosal analgesic will provide relief of the symptoms of pain or discomfort while the oral wound healing agent promotes healing.

F. Statement on Category III Testing Procedures

1. *Comments on study design.* The Panel has agreed that the protocols recommended in this document for the studies required to bring a Category III active ingredient into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved technology in the future.

Experimental design should take into account the need to include a sufficient number of subjects or trials so as to provide meaningful conclusions which can be supported by appropriate statistical analysis. The selection of appropriate subjects or patients is of major importance when the effect of a drug in a specific condition for relief of a specific symptom is under study.

Some bias exists in all situations wherein the subject, the observer, or both make a judgment as to the nature or magnitude of a response. Biological factors also contribute to variation in response between individuals in a given study sample. Although bias and biological variation cannot be eliminated, their effect on the outcome of an experiment can be minimized by adopting a "double-blind, placebo-controlled" or other suitably blinded design. In such a design, one group of subjects receives a placebo or dummy preparation so that the placebo response, unmodified by the conditioning of the test, can be established. In a double-blind study, neither the subjects nor the observer can distinguish the identity of the preparations under test. This requires that the test and placebo preparations be indistinguishable in shape, color, odor, and taste. However, in the case of preparations containing active volatile agents or substances which affect sensory perception, it is impossible to make the placebo indistinguishable from active ingredients. When a placebo is used for comparison, the test medication should exert a quantitatively positive effect which is statistically significant when compared to the placebo. The level of statistical significance which is acceptable is described under each Category III protocol. (See part III, paragraph C, below—Data Required for Evaluation.)

It is often desirable to include as a positive control a standard drug which is known to exert a significant effect against the relevant symptoms being tested. When a standard drug is used for comparison, the test medication should be at least equivalent to the standard.

Finally, the inclusion of two or more dose levels (concentrations) of the drug under test may be desirable in order to provide an estimate of an effective therapeutic dose range which is free from undesirable side effects. If a crossover design is utilized, i.e., each subject serves as his own control, the sequence in which the placebo, standard, and test drugs are administered should be randomized and a sufficient "wash-out period" between tests should be permitted.

Wherever possible, objective measurements should be made in preference to subjective judgments. However, subjective measurements may be required if relevant to the symptom

or symptom complex for which the drug under test is to be used.

2. *Testing period provided for Category III conditions.* The Panel has determined that the available data are insufficient (Category III) to classify some conditions either as Category I or Category II. Such conditions are permitted to remain on the market, or to be introduced into the market, after the date of publication of the final monograph in the **Federal Register,** provided that FDA receives notification of testing in accordance with § 330.10(a)(13) (21 CFR 330.10(a)(13)). The Panel recommends that Category III conditions should be tested within 2 years.

3. *Testing guidelines for Category III combination products.* The Category III active ingredients for the labeling indication claims must be tested in accordance with the evaluation protocol specified for that particular pharmacotherapeutic classification. If, when tested alone, the Category III ingredient or ingredients can be shown to be safe and effective in accordance with the standards for evaluation established in the protocols, it will then qualify for Category I status. The combination will then contain only Category I active ingredients but still must be tested to prove that each ingredient makes a contribution to the product's claimed effect(s).

An acceptable test procedure will be one in which the proposed combination and each of the individual active ingredients at the proposed dosage level in the combination are evaluated, all in the same study, and compared to a placebo for effectiveness against the relevant labeling claim. In this way, it can be shown whether or not each active ingredient in the combination makes a contribution toward effectiveness without incurring an unnecessary decrease in safety.

G. Drug Misuse and Abuse

The potential for development of drug tolerance and addiction due to the use of oral mucosal injury drug products, even when the patient is on an unsupervised regimen, does not seem to exist. However, the Panel believes that misuse of dental care agents occurs when an agent tends to give the subject a false sense of security, thereby diminishing his desire to seek professional advice. When this possibility exists, the label warnings should alert the patient to this danger. The problem becomes especially acute in those cases where the OTC medication suppresses the signs of an infection or other painful symptoms but does not correct the underlying cause. In another example, a person who needs professional dental care may use an OTC dental care agent to enable him to postpone the needed care. Labeling of OTC oral mucosal injury drug products should include warnings against possible misuse of the specific ingredients and should specify a maximum time period for use of the product without the advice of a dentist or physician.

H. Pediatric Considerations

The Panel reviewed the conditions under which dental care products can be safely used by children. Children are defined as individuals under 12 years of age. All of the agents reviewed by the Panel are to be applied topically in the oral cavity and are only inadvertently ingested. For most drugs administered topically, the concentration required for children is equal to that needed by adults. Because the surface area treated may be smaller in a child than in an adult, the total amount of agent applied may be less in a child than in an adult; however, under many circumstances the total amount required by both age groups will be similar. If the adult dosage can be applied safely to children, no special instructions are needed for reduced dosage in children; labeling should, however, indicate that children should be supervised in their use of the agent. If ingestion of an adult dose might cause adverse effects in a child, then the quantity used by the child must be restricted through labeling. In addition, children under 5 years of age cannot be expected to reliably expectorate a dental product (Ref. 1). The dosage for children under 5 years of age must be safe for ingestion; if it is not, labeling should restrict usage to children over 5 years of age.

The Panel recommends packaging in containers with safety closures, additional safety measures whenever necessary and provision of a means for measuring dosage or for single unit dose packaging.

Reference

(1) Barnhart, W. E., et al., "Dentifrice Usage and Ingestion among Four Age Groups," *Journal of Dental Research,* 53:1317–1322, 1974.

I. Inactive Ingredients

A variety of inactive ingredients is used in the manufacture and formulation of products reviewed by the Panel. Such ingredients should be limited to agents that are considered necessary and include abrasives, preservatives, aromatics, vehicles, colorants, sweeteners, anti-oxidants, buffers, and other types of pharmaceutic aids for particular dosage forms.

The Panel did not undertake an extensive review of inactive ingredients because it is the view of the Panel that the safety and the advisability of including specific inactive ingredients in drug products should be reviewed by an appropriate Panel. Since many of these ingredients are used in the formulation of many drug products other than those reviewed by this Panel, it is not appropriate that they be dealt with specifically and solely in relation to dentifrice and dental care agents except when unusual problems arise. This is the case with edetate disodium, which is discussed in the recommendations for Relief of Oral Discomfort Drug Products to be published in a subsequent issue of the **Federal Register.**

For various reasons, individuals may wish to avoid using certain inactive ingredients found in drug products. Such reasons include allergic reactions, previous idiosyncratic responses, safety concerns (whether valid or not), or personal preference. It is impossible to make a free choice in this regard unless all the components of drug products are listed on the labels. Therefore, this Panel strongly recommends that FDA require full ingredient labeling of inactive as well as active ingredients in descending order of quantities present in all drug products. The Panel recognizes that although full disclosure of flavoring and coloring ingredients is desirable, this may be impractical and confusing because of the large number of ingredients which may be involved. Thus, flavoring and coloring ingredients may be listed in accordance with present regulations for labeling such ingredients in food products. The Panel recommends that FDA study the safety of flavorings and colorings, in addition to other inactive ingredients, so that regulations for such ingredients can be devised and applied to all drug products.

J. Single Active Ingredient Products

The Panel has discussed dental combination products earlier in this document. (See part II. paragraph E. above—Principles Applicable to Combination Products.) The Panel concludes that there are some combinations which are rational for concurrent therapy of multiple symptoms for a significant portion of the target population. However, for the individual who has only one condition and needs one ingredient, single active ingredients afford the opportunity to selectively treat such a condition. If a single ingredient is safe and effective for the treatment of a particular symptom, the presence of other ingredients in the

product exposes the patient to additional risk of side effects or idiosyncratic reactions.

Great variability with regard to side effects induced by drugs is seen among patients. Although these side effects and the drugs producing them are sometimes familiar to dentists, physicians, and pharmacists, it is more difficult to determine which ingredient in a combination is causing the side effect. Furthermore, use of fixed combinations, where a single ingredient product would be sufficient, will expose the consumer to additional risk of side effects and allergic reactions without added benefit. These difficulties are largely avoided with single active ingredient products, which many dentists and pharmacists prefer to recommend. There was agreement among Panel members that the availability of products containing single active ingredients would provide increased opportunity for the public and health professionals to select products appropriate to treat the symptoms.

K. Advertising

The Panel is aware that the role of FDA is to regulate labeling of OTC drugs and the role of the Federal Trade Commission is to enforce adherence to such labeling in advertising. In addition to recommending specific labeling claims, warnings, and dosages, the Panel would like to make some general comments and recommendations regarding advertising of drugs.

Advertisements extend the label beyond the pharmaceutical counter or medicine cabinet. The public may well receive most of its attitudes toward dentifrice and dental care agent remedies from advertisements, particularly television advertisements that are often directed toward children.

For this reason the Panel strongly urges the Federal Trade Commission to challenge any advertisement which (1) in any way negates or dilutes the information on the label, especially the contraindications and/or warnings; (2) suggests or leans heavily on words, phrases, and portrayals that lead the lay person to assume that the product is to be used in any manner not recommended in the monograph established below, or that it cures when in reality it only alleviates symptoms; (3) promotes the misuse of the product; (4) advertises either to the lay public or the profession that a product or ingredient is completely tested and proven safe and effective when the Panel has found that insufficient evidence is available to establish general recognition (Category III).

L. General Statements on the Determination of Safety and Effectiveness for OTC Dental Products

The Panel evaluated the safety and effectiveness of OTC dental active ingredients as well as the proper dosage ranges for OTC drug use. In reviewing the scientific literature for these ingredients, the Panel evaluated the available data as to whether or not the ingredient was safe and effective. Among those agents determined to be safe and effective, the Panel did not attempt to determine the drugs of choice for any particular indication.

1. *Determination of safety.* In deciding on the safety of a drug or combination of drugs for the intended use, both animal and human studies were considered. The animal data usually related to levels of the drug that might cause death or cause other serious adverse effects on vital tissues, such as the bone marrow, liver, and kidneys. Also the drug might cause adverse effects on teeth or irritation of the oral mucosa. Animal studies are also helpful in establishing benefit-to-risk ratios for ingredients which are commonly used.

Major attention was paid to information related to adverse drug effects in humans, both adults and children. A knowledge of the toxicology of the drug or drugs under consideration both in animal studies and from human experience make it possible to look specifically for adverse effects in one or more organs or systems. For example, manufacturers of topical anesthetics were required to show that the ingredients used in their products were safe when such ingredients were used in effective concentrations.

It was desirable that there be studies in which the drug was evaluated in its final composition and compared to its vehicle control. However, there were times when the Panel was called upon to make judgments without benefit of controlled pharmacological studies, since they were not available for many ingredients.

2. *Determination of effectiveness.* In determining effectiveness for the intended use, it was necessary to consider each pharmacotherapeutic group separately although certain general principles apply to all groups.

In terms of effectiveness, animal studies were seldom very helpful since it is difficult to find animal models which closely mimic the course of oral diseases and conditions in humans.

Major attention was paid to clinical studies especially where the double-blind technique could be employed. The inclusion of a placebo as a comparison was considered desirable and comparison of the agent with a known standard was also considered useful.

Studies utilizing objective measurements, proper controls, and statistical analysis carried considerable weight in the Panel's decision to place an ingredient in Category I. Certain drug actions make such objective measurements extremely difficult or impossible and, therefore, large well-controlled subjective studies were considered adequate. Partially controlled and uncontrolled clinical studies were of very limited value, but both were considered by the Panel. Clinical experience of a general nature, if documented by qualified experts, added somewhat to the final decision.

The Panel believes that claims of superior effectiveness for one Category I active ingredient over another Category I active ingredient of the same pharmacotherapeutic group should only be permitted on the basis of proven superiority in two or more adequately conducted clinical trials on human subjects by independent investigators comparing the agents directly in the trials. Such claims should not be permitted on the basis of laboratory data.

Misleading superiority claims may also appear as claims that state or imply actions peculiar to a particular product, when in fact those claims are applicable to all OTC drug products or all Category I ingredients of the same pharmacotherapeutic group.

III. Agents for Oral Mucosal Injury

A. General Discussion

1. *General comments.* The Panel recognizes that there is a consumer population which has an occasional need for OTC preparations to treat minor gum disorders such as trauma or irritation of a transient nature. The Panel has classified such preparations as agents for Oral Mucosal Injury. These are agents which relieve oral mucosal injury, e.g., by cleansing or promoting the healing of oral wounds (minor oral irritations). These agents may aid in the formation of new tissue. Agents for relief of oral mucosal injury have been in the marketplace for many years but have not been previously classified as such. Thus, this classification is new and is presented to aid discussion. Without this designation the drugs in this group have been claimed to perform varied and extravagent functions. The creation of the classification has enabled the Panel to recommend specific labeling so that the drugs can stay on the OTC market and be properly used by the consumer. The Panel does

not make any recommendations for professional claims for these products.

Antiseptics and antimicrobials also may possibly aid healing, but the Panel has deferred consideration of these agents to the OTC Advisory Review Panel on Oral Cavity Drug Products. Agents for Oral Mucosal Injury (OMI) are pharmacotherapeutically different from other dental care agents which the Panel classified as Agents for Relief of Oral Discomfort in that OMI agents have no direct effect on oral discomfort, e.g., no anesthetic, analgesic, or protective effect. Agents for the Relief of Oral Discomfort will be discussed in a subsequent issue of the **Federal Register.**

Agents for oral mucosal injury are not intended for use in the treatment of acute or chronic gingival disorders, such as gingivitis and periodontal disease. The Panel concludes that these are conditions which cannot be self-diagnosed and which require professional treatment. These claims have, therefore, been placed in Category II.

2. *Classification.* Panel has further classified agents for oral mucosal injury into oral wound cleansers and oral wound healing agents.

a. *Oral wound cleansers.* These are nonirritating preparations which assist (physically or chemically) in the removal of foreign material from small superficial oral wounds and do not delay wound healing.

Oral wound cleansers are widely used by the lay public and may be recommended by the dental and medical professions for cleansing of wounds caused by trauma, minor dental procedures, and other irritations of the oral soft tissues. Such agents generally contain oxygen-releasing compounds, such as hydrogen peroxide, or other substances which release hydrogen peroxide during use. Upon contact with tissue or salivary catalase and peroxidase, hydrogen peroxide decomposes to form water and oxygen, with resultant foaming action due to release of the oxygen gas. Oral wound cleansing action appears to be a result of this foaming activity, which physically removes debris from the wound. Evidence of effectiveness is based largely on clinical impressions.

b. *Oral wound healing agents.* These are nonirritating agents which aid in the healing of small superficial oral wounds by means other than cleansing and irrigating, or by serving as a protectant.

The general features of wound healing have been known and recognized for centuries, but the exact mechanisms involved are still poorly understood (Refs. 1 and 2). Complications of wound healing following surgery have been markedly reduced, primarily because of control of sepsis, improvements in surgical techniques, and better understanding of nutrition.

Factors involved in wound healing can be divided into two general categories: systemic and local. Systemic factors include (1) physiologic condition of the host, (2) nutrition, and (3) hormones. The local factors include (1) blood and oxygen supply, (2) presence of infection, (3) presence of foreign material, (4) mobility of tissue, (5) amount of tissue destruction, and (6) type of tissue in which injury has occurred (Ref. 3).

The process of wound healing is arbitrarily divided into three overlapping stages: (1) Inflammatory, (2) proliferative, and (3) reorganization or remodeling (Refs. 4 and 5). Many attempts have been made to find substances which would accelerate or modify these stages but none has been generally accepted. However, it is generally considered more important to avoid complications and retardation of wound healing than it is to accelerate the normal, uncomplicated rate of repair (Ref. 6). If, however, promotion of wound healing is claimed for an ingredient, it should have an effect on one or more of the three stages mentioned above.

The inflammatory response stage is ordinarily a necessary prerequisite to wound healing; to shorten this stage would only be beneficial to specific tissues, such as joint articulations where pain and swelling increase as the inflammatory process continues. The value of altering the inflammatory response of oral mucosal injury has not been established.

To modify the proliferative stage by growth stimulation is a highly complex process. While many substances inhibit cell growth without requiring tissue specificity, growth promoters ordinarily have high tissue specificity and require a multitude of co-factors (Refs. 7 and 8). To imply that a substance is a growth promoter when applied to tissues in general is misleading and without a sound and scientific basis.

The stage of reorganization or remodeling depends primarily on the synthesis and metabolism of collagen. Collagen is the main constituent of scar tissue which is the end result of most healing processes in higher vertebrates. This means that tissue repair following injury depends largely on the proper timing, rate of synthesis, and breakdown of collagen molecules, as well as their chemical and structural characteristics (Refs. 9, 10, and 11). Modifying the factors involved in this stage of healing appears to be somewhat realistic and promising (Ref. 12).

In summary, it is expected that an agent which causes promotion of oral wound healing with increase the rate of normal collagen synthesis, producing more rapid clinical improvement.

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B. Categorization of Data

1. *Category I conditions under which agents for oral mucosal injury are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

Category I. Active Ingredients.

The Panel has classified the following agents for oral mucosal injury as active ingredients generally recognized as safe and effective and not misbranded:

Carbamide peroxide in anhydrous glycerin (as an oral wound cleanser)

Hyrogen peroxide in aqueous solution (as an oral wound cleanser)

a. *Carbamide peroxide in anhydrous glycerin.* The Panel concludes that carbamide peroxide in anhydrous glycerin is safe and effective as an oral

wound cleanser for OTC use as specified in the dosage section discussed below.

Carbamide peroxide is unstable in aqueous solution but stable when dissolved in anhydrous glycerin (Ref. 1). Anhydrous glycerin can be prepared by heating Glycerin U.S.P. at 150° C for 2 hours (Ref. 1). Carbamide peroxide in anhydrous glycerin provides a means of delivering hydrogen peroxide to the wound site. On contact with water or saliva in the mouth, carbamide peroxide readily decomposes to form approximately 70 percent urea and approximately 30 percent hydrogen peroxide. In the presence of tissue and salivary catalase and peroxidase, the hydrogen peroxide then breaks down to form water and oxygen.

(1) *Safety.* Clinical use and marketing experience have confirmed that 10 percent carbamide peroxide in anhydrous glycerin is safe for OTC use.

A concentration of 10 percent carbamide peroxide yields approximately 3 percent hydrogen peroxide; this concentration of hydrogen peroxide is within the range the panel considers safe. Glycerin, in the concentration used, and urea, in the concentration generated, are both considered safe (Refs. 2 and 3). In humans, black hairy tongue has been considered by some to be attributable to short term use of carbamide peroxide, but this view is based on a single case report (Ref. 4).

(2) *Effectiveness.* The Panel concludes that 10 percent carbamide peroxide in anhydrous glycerin is effective as an oral wound cleanser.

The principle advantage of carbamide peroxide is that it can be used as a convenient source of hydrogen peroxide. The glycerin reportedly prolongs the release of oxygen from the hydrogen peroxide (Ref. 5), but evidence for prolonged release contributing to effectiveness is not convincing (Refs. 6 through 9).

The Panel, therefore, concludes that 10 percent carbamide peroxide in glycerin is equivalent to approximately 3 percent hydrogen peroxide in effectiveness as an oral wound cleanser. (See part III. paragraph B.1.b.(2) below—Effectiveness.)

(3) *Dosage—Adults and children 2 years of age and older.* Carbamide peroxide 10 percent in anhydrous glycerin.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral mucosal injury active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

(5) *Directions.* 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 physican. Children under 12 years of age should be supervised in the use of this product. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

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b. *Hydrogen peroxide in aqueous solution.* The Panel concludes that hydrogen peroxide in aqueous solution is safe and effective as an oral would cleaner for OTC use as specified in the dosage section discussed below.

(1) *Safety.* Clinal use and marketing experience have confirmed that 1.5 to 3 percent hydrogen peroxide in aqueous solution is safe for OTC use.

Aqueous solutions up to 3 percent of hydrogen peroxide are considered safe for temporary use. This conclusion is supported by animal studies and by extensive human use upon recommendation of the medical and dental professions.

The results of very frequent or prolonged application in animals are conflicting but suggest that irritation may occur (Refs. 1 through 4). Repeated human usage of high concentrations (6 to 30 percent aqueous solution) for a month or more has resulted in gingival pathology and may also cause black hairy tongue (Refs. 4 through 7). Although prolonged use of 3 percent hydrogen peroxide in aqueous solution may produce irritation, the Panel concludes that is safe for OTC use with the recommended labeling discussed below.

(2) *Effectiveness.* The Panel concludes that 1.5 to 3.0 percent hydrogen peroxide in aqueous solution is effective as an oral wound cleanser.

The removal of debris from the wound by the use of hydrogen peroxide is generally recognized by many dental and medical practitioners. A mechanical cleansing effect results from the foaming action of the oxygen bubbles released upon contact with tissue and salivary catalase and peroxidase (Refs. 8, 9, and 10).

There is little experimental evidence to support that the foaming action of the hydrogen peroxide has a beneficial therapeutic effect in terms of faster wound healing.

Consideration of the antiseptic properties of hydrogen peroxide was deferred to the OTC Advisory Review Panel on Oral Cavity Drug Products.

(3) *Dosage—Adults and children 2 years of age and older.* Hydrogen peroxide 3 percent in aqueous solution.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral mucosal injury active ingredients. (See part III, paragraph B.1, below—Category I Labeling.)

(5) *Directions*—(i) *For direct application.* Apply several drops of full strength (3 percent) solution to the affected area of the mouth. Allow the medication to remain in place at least 1 minute and then spit out.

(ii) *For use as an oral rinse.* Mix the full strength (3 percent) solution with an equal amount of warm water. Swish around in the mouth over the affected area for at least 1 minute and then spit out.

(iii) *For direct application and for use as an oral rinse.* Use up to four times daily (after meals and at bedtime) or as directed by a dentist or physician. Children under 12 years of age should be supervised in the use of this product. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

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Category I. Labeling

The Panel recommends the following Category I labeling for oral mucosal injury active ingredients to be generally recognized as safe and effective and not misbranded:

a. *Indications*—(1) *For oral wound cleanser drug products.*

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

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

(2) *For oral wound healing agent drug products.* The Panel has found no Category I labeling indications acceptable at this time and recommends the Category III labeling claim below. (See part III. paragraph B.3. below-Category III Labeling.)

b. *Warnings—For both oral wound cleanser and oral wound healing agent drug products.* (1) "Not to be used for a period exceeding 7 days."

The reason for limiting use to 7 days is that a lack of improvement of an apparent oral mucosal injury may indicate the presence of a serious disease, e.g., cancer or periodontal disease. Continued use of the product may delay diagnosis and treatment of such conditions. The Panel is of the opinion that the available scientific evidence indicates that there are no indications which warrant the use of any oral mucosal injury drug product beyond 7 days except under the advice of a dentist or physician.

(2) "Discontinue use and see your dentist or physician promptly if irritation persists, inflammation develops, or if fever and infection develop."

2. *Category II conditions under which agents for oral mucosal injury are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC oral mucosal injury drug products effective 6 months after the date of publication of the final monograph in the **Federal Register**.

The use of agents for oral mucosal injury under Category II conditions is unsupported by scientific data and, in some instances, by sound theoretical reasoning. The Panel concludes that the Category II active ingredient, dosage form, and labeling should be removed from the market until scientific testing supports their use.

Category II. Active Ingredient

The Panel has classified the following active ingredient for oral mucosal injury as not generally recognized as safe and effective or as misbranded:

Sodium perborate monohydrate (as a wound cleanser)

a. *Sodium perborate monohydrate.* The Panel concludes that sodium perborate monohydrate as a source of hydrogen peroxide is not justified for OTC use as an oral wound cleanser based on an unfavorable risk-to-benefit ratio.

Sodium perborate monohydrate ($NaBO_3H_2O$) (a synonym for sodium peroxyborate (NaBO2H202) monohydrate) releases hydrogen peroxide when dissolved in water. While the Panel concludes that aqueous hydrogen peroxide 1.5 to 3.0 percent is safe and effective as an oral wound cleanser, the Panel is aware that the concentrations of sodium perborate monohydrate that would be effective for OTC use as an oral wound cleanser are not safe. The amount of boron contained in one unit-of-use (1.2 g) package for preparation of a single oral rinse exceeds the maximum safe daily amount of boron for ingestion; the resulting solution releases a concentration of hydrogen peroxide less than the Panel's minimal effective concentrations. Furthermore, safety in regard to lack of tissue irritation by solutions of sodium perborate monohydrate remains to be established.

(1) *Safety.* Gleason et al. (Ref. 1) state that the toxicological aspects of the sodium perborates cannot be distinguished from those of sodium borate and boric acid, the toxicity of which has been thoroughly studied (Refs. 2 through 26). The Panel concludes that the maximum safe dosage of boron for adult humans is 0.09 g daily (Refs. 1 through 16, and 21).

On a chemical basis, boron (atomic weight 10.8) is approximately 10.8 percent of the sodium perborate monohydrate molecule (molecular weight 99.8). A single unit-of-use package of a buffered sodium perborate monohydrate oral rinse reviewed by the Panel contains approximately 1.2 g sodium perborate monohydrate (boron content of approximately 0.13 g) to be dissolved in 30 ml (1 oz) of water just prior to use as an oral rinse (Ref. 27). Oral wound cleansers containing peroxide are generally used up to four times daily; four such 30 ml rinses contain 0.52 g of boron, and if that amount were inadvertently totally ingested, the consumer would receive nearly six times the amount safe for daily ingestion.

In a recent study, one of the subjects who followed the manufacturer's directions for use of four daily rinses failed to expectorate (and therefore was presumed to have swallowed) 60 mg boron (two-thirds the maximum safe daily amount). However, the above rinse (containing approximately 3.3 percent sodium perborate, equivalent to approximately 4 percent sodium perborate monohydrate) yields a hydrogen peroxide concentration concluded by the Panel to be subtherapeutic (see below).

Although the sodium perborate monohydrate oral rinse reviewed by the Panel is buffered by sodium bitartrate, it is still quite alkaline, approximately pH 9 (Ref. 27). The potential irritancy of this formulation to the oral mucosa has not been adequately determined for the concentrations which are currently recommended by the manufacturer (equivalent to 4 percent sodium perborate monohydrate). In early studies designed to evaluate effectiveness, oral mucosal irritation was noted within 2 to 7 days when concentrations of approximately twice the manufacturer's presently recommended concentrations were used three to five times daily. While no irritation was noted in later studies conducted over a longer period of time, the concentration employed in these later studies was only one-half that presently recommended by the manufacturer.

(2) *Effectiveness.* When dissolved in water, 34 percent of the sodium perborate monohydrate molecule becomes available as hydrogen peroxide. If 1.2 g sodium perborate monohydrate is dissolved in approximately 30 mL (1 oz) of water as presently recommended (Ref. 27), a concentration of 1.3 percent hydrogen

peroxide is obtained. This concentration of hydrogen peroxide is below the 1.5 percent minimum which the Panel considers to be effective as an oral wound cleanser. (See part III. paragraph B.1.b.2. above—Effectiveness.)

(3) *Evaluation.* An oral rinse containing approximately 4.0 percent sodium perborate (obtained by dissolving 1.2 g sodium perborate monohydrate and a buffer in 30 mL water) yields a concentration of 1.3 percent hydrogen peroxide, which is less than the Panel's minimum concentration (1.5 percent) for hydrogen peroxide as an effective oral wound cleanser. If four such 30 mL rinses were inadvertently totally ingested in a day, the amount of boron ingested would be nearly six times the amount concluded by the Panel to be safe for daily ingestion. If the concentration of sodium perborate monohydrate were increased to yield a therapeutic concentration of hydrogen peroxide when the salt is dissolved in water, the risk of boron toxicity would also be increased. The Panel, therefore, concludes that the risk of boron toxicity that may be incurred by use of concentrations of sodium perborate monohydrate sufficient to yield therapeutic concentrations of hydrogen peroxide is unjustified by benefit, if any, from use of the salt as a source of hydrogen peroxide. Furthermore, safety from irritancy of oral mucosa has not been established.

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Category II. Dosage Form

The Panel has reviewed several dentifrice formulations containing ingredients which have been classified as agents for oral mucosal injury. A dentifrice is intended to be used on a toothbrush. The Panel concludes that use of a dentifrice dosage form is irrational in the treatment of oral wounds because additional trauma may result from the toothbrushing. In addition, a dentifrice usually contains an abrasive, and abrasivity of the dentifrice may also interfere with healing. This effect, however, is not as harmful as the harmful effect of the toothbrushing itself on the wound.

The Panel also notes that some dentifrices have been marketed for the treatment of gingivitis. The Panel has placed all claims stating or implying prevention, control, or treatment of gingivitis in Category II. Therefore, any dentifrice, whether promoted as an agent for oral mucosal injury or gingivitis, is Category II.

Category II. Labeling

The Panel concludes that the use of certain labeling claims related to the safety and/or effectiveness of a product are unsupported by scientific data and, in some instances, by sound theoretical reasoning. The Panel concludes that such labeling should be removed from the market.

The Panel concludes that drug products which have antiplaque, plaque control, or gingivitis claims are not currently appropriate for the OTC market because there is no general recognition of any such drug products as safe and effective for these indications at this time. Accordingly, the Panel recommends that such drug products and claims should be evaluated by FDA through the NDA procedure.

a. *Oral wound cleansers.* The Panel concludes that the following indications should not be cited for the use of oral wound cleansers because the terms are vague to the consumer; the conditions described cannot be self-diagnosed; they are serious; and self-treatment of these conditions may delay diagnosis: "aphthous ulcers," "canker sores," "periodontal disease," and "pyorrhea."

The Panel also concludes that pain relief is not a direct benefit obtained from an oral wound cleanser and, therefore, is not an acceptable indication or claim. Some examples of such labeling follow: "relieves pain * * *," "temporary relief of minor congestion and associated pain of surface inflammation," "temporary relief of distress," and "apply before a meal for pain relief."

The Panel further concludes that prevention of inflammation is not a direct benefit of oral wound cleansing and, therefore, should not be stated as either an indication or as a claim. Some examples of such labeling follow: "prophylaxis of oral inflammation" and "prevention of minor inflammation."

Since oral wound cleansers should not be used for more than 7 days without professional supervision, their use as "an aid to regular oral hygiene" is not an acceptable indication.

Additionally, the Panel believes that the direction to "massage the medication on affected area" is inappropriate since there is no evidence that massage of damaged tissue is beneficial.

The Panel concludes that in addition to the labeling citing above the following statements are not acceptable:

(1) "Not known to be irritating or sensitizing" because it implies that such reactions will never occur.

(2) "Promotes firmer and healthier gums" because therapeutic benefit has not been demonstrated and the term implies long-term OTC use beyond 7 days.

(3) "Cleanser * * * with a * * * microfoam" because the term is vague and may be misleading.

b. *Oral wound healing agents.* The Panel concludes that oral wound healing agents do not contribute directly to the relief of soreness, pain, or discomfort and that these latter terms are, therefore, not acceptable indications. In addition, the Panel believes that statements such as "clinically tested" or "hospital tested" may cause the consumer to assume that effectiveness has been established unequivocally and that other Category I ingredients are not "clinically tested." Such statements, therefore, are misleading. The phrase "assists nature" is considered ambiguous, would be difficult to prove, and is not acceptable.

c. *Oral wound cleansers and wound healing agents.* The Panel concludes that the term "gum inflammation" describes a manifestation of gingivitis or may indicate the presence of periodontal disease. These are serious conditions which require the treatment and supervision of a dentist or physician as soon as possible since these conditions cannot be self-diagnosed by the consumer.

The term "oral discomfort" is also classified as Category II when associated with oral mucosal injury agents. These agents may only indirectly provide relief of discomfort and are intended to act directly either as a cleanser or wound healing agent. Agents for relief of oral discomfort, to be discussed in a later issue of the **Federal Register**, include such direct action agents as local anesthetics.

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

The Panel concludes that adequate and reliable scientific evidence is not available at this time to permit final classification of the ingredients and conditions listed below. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within 2 years, however, the ingredients and conditions listed in this category should no longer be marketed in OTC products. The Panel recognizes that these products have been available for a number of years without reports of serious side effects. Therefore, safety testing guidelines need not conform to those necessary for new drugs as noted elsewhere in this document. However, since oral wound healing agents are not products generally recognized as existing in the OTC marketplace, the Panel concludes that testing must provide safety and effectiveness when applicable.

Category III. Active Ingredients

The Panel concludes that the available data are insufficient to permit final classification of the following active ingredients for oral mucosal injury:

Allantoin (as a wound healing agent)

Carbamide peroxide in anhydrous glycerin (as a wound healing agent)

Chlorophyllins, water-soluble (as a wound healing agent)

Hydrogen peroxide in aqueous solution (as a wound healing agent)

a. *Allantoin.* The Panel concludes that allantoin is safe but that there are insufficient data available to permit final classification of its effectiveness for OTC use as an oral wound healing agent as specified in the proposed dosage section discussed below.

(1) *Safety.* Clinical use and marketing experience have confirmed that 2 percent allantoin is safe for OTC use.

Allantoin is a drug which has been used as a growth stimulant since 1912 (Refs. 1 and 2). A review published in 1946 (Ref. 3) indicated that allantoin had been marketed in concentrations of 0.4 to 2 percent, often in combination with chemotherapeutic agents and/or other medications. Such preparations were usually in ointment, solution, or powder form and were intended primarily for topical application to the skin and mucous membranes. The indications were mainly the healing of suppurating wounds, burns, abscesses, and ulcers, as well as a wide variety of skin conditions. Adverse reports have not been found in the literature and an evaluation published in 1972 stated that no skin reactions had been reported (Ref. 4). One report indicated that allantoin in solution was painless when applied to wounds (Ref. 5). When large doses have been administered orally, intramuscularly, or intravenously to experimental animals and man, a leucocytosis response has been reported to occur (Refs. 6 and 7).

The Panel has designated allantoin in concentrations of up to 2 percent as safe for topical application to oral mucous membranes because of its long history of topical use without apparent toxicity or other undesirable effects.

(2) *Effectiveness.* The literature indicates that allantoin was most widely used as a growth stimulant in the period of 1930 to 1950 (Refs. 3, 5, and 7 through 18). Unfortunately, in the majority of these reports, effectiveness was based on clinical impression in which modern double-blind controlled, experimental design was not employed. There have been a few more recent studies, but these also lack well-designed protocols to document effectiveness (Refs. 19 through 22). Because the evidence in the literature is insufficient to demonstrate effectiveness, the Panel concludes that more data are needed to prove that allantoin promotes healing, and contributes significantly to healing when incorporated into a combination with other agents.

(3) *Proposed dosage. Adults and children 2 years of age and older.* Allantoin 0.4 to 2.0 percent.

(4) *Labeling.* The Panel recommends the Category III labeling specified below. (See part III. paragraph B.3. below—Category III Labeling.)

(5) *Directions.* Apply directly to affected area. Use up to four times daily after meals and at bedtime or as directed by a dentist or physician. Children under 12 years of age should be supervised in the use of this product. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(6) *Evaluation.* Data to demonstrate effectiveness as an oral wound healing agent will be required in accordance with the guidelines set forth below. (See part III. paragraph C. below—Data Required for Evaluation.)

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b. *Carbamide peroxide in anhydrous glycerin.* The Panel concludes that carbamide peroxide in anhydrous glycerin is safe but that there are insufficient data available to permit final classification of its effectiveness for OTC use as an oral wound healing agent as specified in the proposed dosage section discussed below.

(1) *Safety.* Clinical use and marketing experience have confirmed that 10 percent carbamide peroxide in anhydrous glycerin is safe for OTC use. The safety of the ingredient is discussed earlier in this document. (See part III. paragraph B.1.a.(1) above—Safety.)

(2) *Effectiveness.* When peroxides are brought into contact with the abundant catalases and peroxidases of the oral environment, the release of oxygen from peroxide is rapid and of fleeting duration. Moreover, the quantity of oxygen released by therapeutically safe concentrations is small. Ten percent carbamide peroxide yields approximately 3.0 percent hydrogen peroxide which further yields approximately 1.4 percent oxygen. Whether such relatively low transient concentrations of oxygen increase tissue pO_2 (oxygen partial pressure, i.e., oxygen tension) to promote wound healing has not been adequately determined.

While in vitro microrespirometry, visual inspection, and subjective histological evaluations have suggested that topically applied peroxides may aid wound healing by increasing the oxygen consumption of tissues (Refs. 1 through 6), these methodologies are either obsolete or too subjective to be reliable. Microelectric methods are now used to determine the role of various oxygen concentrations in tissue metabolism (Refs. 7 and 8). These methods, which permit direct measurement of oxygen tension in the liquid phase, are more sensitive and accurate than microrespirometry for a variety of reasons reviewed by Clark and Sachs (Ref. 9). Moreover, ultramicroelectrodes can be used in vivo; such studies have documented that a pO_2 gradient occurs between a wound and an adjacent capillary (Ref. 10). Further refinements for studying the role of oxygen in wound healing in vivo have included radiometric monitoring of pO_2 in surgically created wound dead-spaces (Refs. 10 and 11) as well as in silastic tubing tonometers (Ref. 12). Such tudies have shown that protein synthesis, including the synthesis of connective tissue and collagen, increases in "hyperoxic" conditions (40 to 70 percent oxygen as compared with the 20 percent oxygen present in air); bone repair decreases in such concentrations and increases only in "hypoxic" conditions of about 14 percent oxygen (Refs. 13 through 18). Similar studies are needed to determine whether the concentration of oxygen obtained from 10 10 percent carbamide peroxide significantly increases tissue pO_2 and whether such an increase correlates with accelerated connective tissue and collagen synthesis. The tissue pO_2 determination must be done by the use of modern technology rather than by microrespirometry.

(3) *Proposed dosage—Adults and children 2 years of age and older.* Carbamide peroxide 10 percent in anhydrous glycerin.

(4) *Labeling.* The Panel recommends the Category III labeling specified below. (See part III. paragraph B.3. below—Category III Labeling.)

(5) *Directions.* Apply directly to affected area. Use up to four times daily after meals and at bedtime or as directed by a dentist or physician. Children under 12 years of age should be supervised in the use of this product. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(6) *Evaluation.* Data to demonstrate effectiveness as an oral wound healing agent will be required in accordance with the guidelines set forth below. (See part III. paragraph C. below—Data Required for Evaluation.)

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c. *Chlorophyllins, water-soluble.* The Panel concludes that chlorophyllins, water-soluble, are safe but that there are insufficient data available to permit final classification of effectiveness for OTC use as an oral wound healing agent as specified in the proposed dosage section discussed below.

Chlorophyllins, water-soluble, are also known as potassium-sodium-copper chlorophyllin and water-soluble derivatives of chlorophyll.

(1) *Safety.* Potassium-sodium-copper chlorophyllin is a water-soluble, saponified, metal complex derivative of chlorophyll "a". The Panel concludes that this compound is safe based on reports that 100 to 200 mg daily have been ingested by sizable groups of people for 3 months to 1 year with no deleterious effects (Refs. 1, 2, and 3). A small group of patients given 500 mL of a 0.5 percent solution daily, intravenously, for 8 days in cases of subacute bacterial endocarditis developed no toxic symptoms (Ref. 1). Furthermore, topical application for treatment of leg ulcers (Ref. 4) and for wound healing after a variety of surgical procedures (Ref. 5) has caused no apparent skin irritation. Similarly, oral use of this compound has not produced undesirable side effects (Refs. 6 through 10). Finally, no toxicity was found in rats fed potassium-sodium-copper chlorophyllin for 2 years (Ref. 9).

(2) *Effectiveness.* While the mechanisms whereby water-soluble chlorophyllin produces its effect have not been defined, the medical literature contains numerous accounts of wounds and ulcerations that did not respond to other attempts to induce healing, but that did heal with chlorophyllins therapy. These accounts are anecdotal, however, and must be substantiated in adequate well-controlled studies.

Some investigators have demonstrated that water-soluble chlorophyllin stimulates the growth of fibroblasts in in vitro tissue culture (Ref. 11) and that chlorophyllin exerts a bacteriostatic effect on organisms found on oral mucosa and produces a decrease in the acid production of saliva (Ref. 12). In vivo studies include the investigation of wound healing in animals (Ref. 1) and the measurement of the decline of electrical potential during the healing process (Ref. 13). The latter procedure has been employed as an index to the rate of healing in experimental abrasions of humans.

(3) *Proposed dosage—Adults and children 2 years of age and older*—(i) *Solution:* Chlorophyllins, water-soluble, 0.2 percent in a buffered saline solution (pH 7.3 to 8.5).

(ii) *Ointment:* Chlorophyllins, water-soluble, 0.5 percent in a suitable base.

(4) *Labeling.* The Panel recommends the Category III labeling specified below. (See part III. paragraph B.3. below—Category III Labeling.)

(5) *Directions.* Apply directly to affected area. Use up to four times daily after meals and at bedtime or as directed by a dentist or physician. Children under 12 years of age should be supervised in the use of this product. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(6) *Evaluation.* Data to demonstrate effectiveness as an oral wound healing agent will be required in accordance with the guidelines set forth below. (See part III. paragraph C. below—Data Required for Evaluation.)

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d. *Hydrogen peroxide in aqueous solution.* The Panel concludes hydrogen peroxide in aqueous solution is safe but that there are insufficient date available to permit final classification of its effectiveness for OTC use as an oral wound healing agent as specified in the proposed dosage section discussed below.

(1) *Safety.* Clincal use and marketing experience have confirmed that 1.5 to 3.0 percent hydrogen peroxide in aqueous solution is safe for OTC use. The safety of the ingredient is discussed

earlier in this document. (See part III. paragraph B.1.b.(1) above—Safety.)

(2) *Effectiveness.* The effectiveness of hydrogen peroxide as an oral wound healing agent is related to the effectiveness of peroxide as discussed under carbamide peroxide in anhydrous glycerin. (See part III. paragraph B.3.b.(2) above—Effectiveness.) There is insufficient evidence to establish effectiveness for this claim.

(3) *Proposed dosage—Adults and children 2 years of age and older.* Hydrogen peroxide 3 percent in aqueous solution.

(4) *Labeling.* The Panel recommends the Category III labeling specified below. (See part III. paragraph B.3. below—Category III Labeling.)

(5) *Directions*—(i) *For direct application.* Apply several drops of full strength (3 percent) solution to the affected area. Allow the medication to remain in place at least 1 minute and then spit out.

(ii) *For use as an oral rinse.* Mix the full strength (3 percent) solution with an equal amount of warm water. Swish around in the mouth over the affected area for at least 1 minute and then spit out.

(iii) *For direct application and for use as an oral rinse.* Use up to four times daily after meals and at bedtime or as directed by a dentist or physician. Children under 12 years of age should be supervised in the use of this product. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(6) *Evaluation.* Data to demonstrate effectiveness a an oral wound healing agent will be required in accordance with the guidelines set forth below. (See part III. paragraph C. below—Data Required for Evaluation.)

Category III. Labeling

The Panel concludes that the following labeling claims for oral wound cleansers or oral wound healing agents are presently unsupported by sufficient scientific data to permit classification in Category I. Additional data are required as indicated elsewhere in this document. (See part III. paragraph C. below—Data Required for Evaluation.)

a. *Oral wound cleansers.* The claim of "Longer oxygen action" (Ref. 1) must be established by quantitative chemical analysis. Visual estimations of intensity and height of frothing (Refs. 1 through 4) are too imprecise to be acceptable.

b. *Oral wound healing agents.* "For temporary use to aid healing of minor oral soft tissue wound due to injury."

Labeling should not use the term "oxygenating" or otherwise imply that peroxides aid wound healing by increasing tissue oxygen consumption unless a substantial increase in tissue pO_2 (oxygen partial pressure, i.e., oxygen tension) can be demonstrated by modern methodology. If a significant increase in oxygen uptake cannot be demonstrated when safe concentrations of peroxides are applied, the therapuetic benefit of peroxides may be attributed only to the mechanical removal of necrotic tissue and oral debris, as discussed under oral wound cleansers.

References

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C. Data Required for Evaluation

The Panel has agreed that the guidelines recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. *General principles in the design of an experimental protocol for testing oral mucosal injury ingredients.* The effectiveness of an oral mucosal injury ingredient is dependent on its ability to act as an oral wound cleanser or as an oral wound healing agent. In order to move from Category III to Category I, the appropriate set of testing procedures identified below must be performed and found to be statistically significant in safety and effectiveness.

a. *Oral wound healing agents.* Wound healing is not an isolated, single phenomenon, but a series of complex biologic events. It involves such processes as platelet aggregation and blood clotting; an inflammatory response; alterations in the ground substance; endothelial and capillary proliferation; fibroblastic proliferation and collegen production; epithelial proliferation and surface covering (Ref. 1).

Several animal models have been employed to study wound healing. These include (1) wounds of incision of excision; (2) wound creating artificial dead spaces, e.g., polyvinyl sponges, stainless steel wire mesh cylinders; (3) wounds resulting from insertion or injection of agents causing a sterile inflammatory response, e.g., carageenin or turpentine; (4) burn wounds; and (5) wounds caused by ionizing radiation and light, e.g., X-rays, ultraviolet, or laser (Ref. 1)

Healing is not complete until the disrupted surfaces are firmly bound by scar tissue (which is the end result of most healing processes), and there is a complete surface covering implying return of function. Therefore, any measure of the rate of wound healing is a measure of the rate of epithelialization and of collagen synthesis.

The following tests are suitable for testing of oral wound healing agents. The Panel recommends that at least one skin model and one oral mucosal model be used to test the ingredient.

(1) *Skin models*—(i) *Measurement of the rate of wound closure and epithelialization.* A suggested model to study the rate of epithelialization using an excision wound is based upon the model described by Lorenzetti, Fortenberry, and Busby (Ref. 2). Excision wounds are made in a test animal with a sharp scalpel under surgically clean conditions. The area and the depth of the wound are to be kept constant using a template and confirming the excision by measurement as one proceeds with the surgery. When bleeding is under control, the wound margins are traced onto Blenderm™ tape (3M Company, Minneapolis, Minnesota) for a measurement. At this point, the test material is applied to the wound and covered with an appropriate bandage for protection; similar excised untreated wounds will serve as controls.

Wounds should be examined under blind conditions every 2 to 4 days. Measurement of the size of the wound is made by placing Blenderm tape over the wound and tracing the advancing edges of new epidermal growth with a marking pencil. The tape is then transferred to a paper where the area is traced and appropriate measurements can be made. The percent closure of the wounds from the initial wound areas is to be recorded. To compare the different test treatments, analyses of variances should be done to determine differences between tests on the same animal and differences between animals, as well as differences between dressings on different days, especially if different observers were used. For individual analysis on any one day, a *t* test can be used.

(ii) *Wound collagen formation and maturation.* Collagen metabolism is intimately associated with tissue regeneration and remodeling. The synthesis of new collagen may be

normal or defective; if defective, it will lead to incomplete healing of wounds or to excessive scar formation, both of which depend largely upon the nature of the collagen fibers as determined by the biosynthesis and maturation of the collagen molecule.

The synthesis and maturation of collagen is a complex phenomenon. There are a number of modifications of the molecule which occur after the constituent amino acids have been incorporated into peptide linkages. One modification is the hydroxylation of proline and lysine; another is the glycosylation of hydroxyglysine with galactose and the subsequent glycosylation of some of the galactosylhydroxylysine residues with glucose. Finally, the introduction of covalent cross-links, both intra- and intermolecularly, is the last step which the collagen molecule undergoes before becoming structual connective tissue.

A measure of this complex phenomenon from synthesis of collagen to its complete maturation in tissues is performed by (1) determining salt-soluble collagen, as a measure of newly synthesized collagen, (2) weak organic acid-soluble collagen, as a measure of collagen in transition from newly synthesized to completely mature collagen, and (3) insoluble collagen, as a measure of completely matured and cross-linked collagen.

Using the model system described from the determination of wound closure and epithelialization, the rate and maturation of collagen can be determined. Wounds treated with test materials can be analyzed for the progress of collagen maturation following wounding procedures.

Collagen and the state of the collagen molecule after wounding can be determined chemically by the method of Prockop and Udenfriend (Ref. 3), radiochemically by the method of Aleo, Novak, and Levy (Ref. 4), or the method of Diegelmann, Rothkopf, and Cohen (Ref. 5). The final data should represent (1) absolute and relative collagen synthesis, (2) relative rate of collagen synthesis, and (3) the extent of proline hydroxylation in treated and untreated wound tissue.

(2) *Animal oral mucosal models (oral cavity of dogs)*—(i) *Punch biopsy model.* Two independent investigators should separately test oral wound healing agents on sufficient numbers of beagle dogs to obtain a statistically significant result. It is suggested that at least ten young, healthy dogs of either sex be studied by each investigator using a crossover design for study of active medication in vehicle compared to vehicle without medication.

Dogs are randomly assigned, half to the active group and half to the placebo. Under local anesthesia, a 5 mm punch biopsy lesion is made in a standard area of oral mucosa on one side (the bicuspid area avoiding the line where the teeth incise would be suitable). After hemorrhage is stopped, the dog is returned to its cage and medication or placebo (randomly numbered with a three digit number according to assignment) is applied after 6 hours and subsequently 3 to 4 times daily at 4 to 6 hour intervals for 7 days. A rinse with warm water is used before each treatment.

The dog is examined daily for measurement of lesion size by a plastic lesion matrix. After 6 weeks the dog receives a second wound on the other side of its mouth in the same area and the paired medication treatment is used.

Mean lesion size for each treatment is calculated and statistically analyzed. The active medication should be statistically better than the placebo and should demonstrate an effect in the first 7 days.

(ii) *Other methods.* Industry and FDA are encouraged to develop other models to measure wound healing effectiveness. The Panel suggests that mucosal abrasion models currently used by FDA to test oral mucosal irritation may be adapted to measure wound healing effectiveness.

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b. *Oral wound cleansers.* The Panel concurs with the testing procedures for skin wound cleansers stated in the tentative final monograph on OTC Topical Antimicrobial Products published in the **Federal Register** of January 6, 1978 (43 FR 1210) and has utilized these procedures with appropriate modifications.

Inherent in the product's definition is a demonstration of its ability to assist in the cleansing and removal of foreign material while causing no delay in wound healing. In addition, cleansing ingredients which are classified as "peroxides" must be able to release oxygen at the wound site.

The Panel recognizes that the testing of delay in wound healing, particularly in human subjects, is difficult. There is a need for the development of procedures to determine whether topical wounds would delay healing in human subjects. Until adequate human testing procedures are available, data from animal models will be required to support safety of a product to be labeled as an oral wound cleanser.

(1) *Animal test for delay in wound healing.* The Panel concludes that one of the following animal tests should be used to evaluate and compare the oral wound healing delay effects of oral wound cleansers:

(i) The subjects should consist of 12 young adult male New Zealand rabbits. Both antimicrobial-treated and antimicrobial-untreated control animals should be used.

(ii) The back of the rabbit should be shaved so that approximately 20 percent of the total body surface area is shaved.

(iii) The investigator should make a wound by dermal incision in the shaved area 24 hours after clipping. A sterile technique must be followed in making the dermal incision. Next, the area should be washed with 70 percent isopropyl alcohol solution. Using a scalpel, six 1-inch long freehand incisions, three on each side of the midline, approximately 0.5 to 1 mm deep, should be made through the dorsal skin. These incisions should be full thickness wounds. One-half of the wounds (three incisions) should be sutured. Treatments should begin within 1 hour after wound inducement.

The three treatment conditions should be tap water, an aqueous solution of the wound cleansing agent, and no treatment. Solutions should be prepared daily in tap water immediately before use. Each set of two incisions (1 sutured and 1 nonsutured wound) should be subject to one of the treatments. One mL of solution should be gently applied for 1 to 2 minutes daily for 14 consecutive days. These daily applications should be 6 hours apart. The applied material should be allowed to dry. After the initial application, each incision should be rinsed with tap water immediately prior to subsequent treatments and gently dried. The animals should wear collars throughout the study to prevent oral ingestion of test material.

(iv) To evaluate the test the following parameters should be utilized: Body weight should be determined for each rabbit on days 0, 7, and 14; wound-

healing progress and general conditions should be observed and described daily. This is to be supplemented by color photographs. Two animals each should be sacrificed on days 1, 3, 5, 7, 10, and 14 by air injection. Wound sections should be evaluated and compared microscopically.

(2) *Evaluation of oral wound cleansers in humans.* The Panel was not able at this time to develop a generally acceptable procedure for evaluating of oral wound cleansers and recommends that the industry and FDA consider suitable methods. The following techniques have been used for other purposes and may have some application in evaluation oral would cleansers:

(i) Determination of leucocytes in the oral rinse; an increase in the number of leucocytes compared to those obtained from a tap water rinse indicates more efficient wound cleansing. A technique for determining leucocytes in oral fluid was described by Klinkhamer (Ref. 1) and by Wright (Ref. 2).

(ii) Determination of desquamated epithelial cells from paraffin stimulated saliva. The subject rinses with an active ingredient test product or a control and removes the rinse fluid. Then paraffin in simulated saliva is collected for 5 minutes. Desquamated epithelial cells are determined from a histological slide of the saliva. An effective wound cleanser will result in a lower count of desquamated epithelial cells than the control.

(iii) Buccal scrapings of the wound are made after rinsing, an effective wound cleanser shows less desquamated epithelial cells than scrapings taken from wounds after the control rinse.

References

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(2) Wright, D. E., "Leucocytes in the Saliva of Edentulous and Caries Free Subjects," *Archives of Oral Biology*, 7:581–585, 1962.

The Food and Drug Administration has determined that this document does not contain an agency action covered by 21 CFR 25.1(b) and consideration by the agency of the need for preparing an environmental impact statement is not required.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under authority delegated to the Commissioner (21 CFR 5.1), it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended by adding new Parts 353, to read as follows:

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

Subpart A—General Provisions

Sec.

Subpart B—Active Ingredients

Subpart C—[Reserved]

Subpart D—Labeling

Authority: Secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371); (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—General Provisions

§ 353.1 Scope.

An over-the-counter oral mucosal injury drug product in a form suitable for topical administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this Part 353 and each of the general conditions established in § 330.1 of this chapter.

§ 353.3 Definitions.

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

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

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

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

Subpart B—Active Ingredients

§ 353.10 Oral mucosal injury active ingredients.

The active ingredients of the product consist of the following when used within the concentration established for each ingredient:

(a) *Oral wound cleansers.* (1) Carbamide peroxide 10 percent in anhydrous glycerin.

(2) Hydrogen peroxide 3 percent in aqueous solution.

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

§ 353.20 Permitted combinations of active ingredients.

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

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

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

Subpart C—[Reserved]

Subpart D—Labeling

§ 353.50 Labeling of oral mucosal injury products.

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

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

(1) *For oral wound cleanser drug products.* (i) "For temporary use in the cleansing of wounds caused by minor oral irritation or injury such as following minor dental procedures, or from dentures or orthodontic appliances."

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

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

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

(1) *For products containing any ingredient identified in § 353.10(a) and (b).* (i) "Not to be used for a period exceeding 7 days."

(ii) "Discontinue use and see your dentist or physician promptly if irritation persists, inflammation develops, or if fever and infection develop."

(2) [Reserved]

(d) *Directions.* The labeling of the product contains the following statements under the heading "Directions," followed by "or as directed by a dentist or physician."

(1) *For products containing carbamide peroxide identified in § 353.10(a)(1).* 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 physician. Children under 12 years of age should be supervised in the use of this product. For children under 2 years of age, there is no recommended dosage except under the advise and supervision of a dentist or physician.

(2) *For products containing hydrogen peroxide identified in § 353.10(a)(2)*—(i) *For direct application.* Apply several drops of full strength (3 percent) solution to the affected area of the mouth. Allow the medication to remain in place at least 1 minute and then spit out. Use up to four times daily after meals and at bedtime or as directed by a dentist or physician. Children under 12 years of age should be supervised in the use of this product. For children under 2 years of age, there is no recommended dosage except under the advise and supervision of a dentist or physician.

(ii) *For use as an oral rinse.* Mix the full strength (3 percent) solution with an equal amount of warm water. Swish around in the mouth over the affected 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 physician. Children under 12 years of age should be supervised in the use of this product. For children under 2 years of age, there is no recommended dosage except under the advise and supervision of a dentist or physician.

Interested persons are invited to submit their comments in writing (preferably in four copies and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal on or before January 24, 1980. Comments should be addressed to the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857, and may be accompanied by a supporting memorandum or brief. Comments replying to comments may also be submitted on or before February 25, 1980. Comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

In accordance with Executive Order 12044, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of the regulatory analysis assessment supporting this determination is on file with the Hearing Clerk, Food and Drug Administration.

Dated: October 1, 1979.

Sherwin Gardner,

Acting Commissioner of Food and Drugs.

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