DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

21 CFR Part 355

[Docket No. 80N-0042]

Anticaries Drug Products for Over-the-Counter Human Use Establishment of a Monograph; Notice of Proposed Rulemaking

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: This proposed rule would establish conditions under which over-the-counter (OTC) anticaries drug products (products which aid in the prevention of dental caries (decay or cavities)) 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 June 26, 1980, and reply comments by July 28, 1980.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-62, 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 July 13, 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 Commissioner of Food and Drugs is issuing: (1) a proposed regulation containing the monograph recommended by the Panel, which establishes conditions under which OTC anticaries 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 these 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.

The Panel recommended that certain fluoride dental rinses and gels, which have previously been restricted to prescription use, be made available OTC provided that they contain no more than 120 mg total fluorine, and that they are packaged in containers with child-resistant closures. Without addressing the merits of this recommendation, the agency merely wishes to point out that no final decision will be made without careful and thorough evaluation of all comments submitted in response to the publication of this proposal. FDA is especially interested in receiving comments and data on the issue of whether these fluoride gels and rinses offer any added benefit to persons who also use a fluoride dentrifice daily, who live in areas where optimal fluoride levels are present in the water supply, and who may also be given professionally applied fluoride treatments periodically. Any person marketing one of these products OTC prior to publication in the **Federal Register** of a final monograph will do so at his or her own risk, as detailed in § 330.13 (21 CFR 330.13). While FDA does not have the authority to require child-resistant closures, manufacturers are urged to voluntarily comply with the Panel's recommendations. FDA will make the Consumer Product Safety Commission, the agency responsible for regulating child-resistant packaging, aware of the Panel's recommendations.

The agency is also aware of the Panel's recommendations in the Panel's report regarding final formulation testing, i.e., "Laboratory Testing Profiles," of Category I active ingredients formulated in a dentifrice (abrasive-containing) dosage form. The Panel's final formulation recommendations represent a new concept with many technical issues yet to be resolved; therefore, they have not been included as part of the proposed monograph, although the recommendations are in the Panel's report.

After FDA has carefully reviewed all comments submitted in response to this proposal, the Commissioner will issue a tentative final regulation in the **Federal Register** to establish a monograph for OTC anticaries drug products. The agency will determine at that time if the Panel recommendations on final formulation testing should be included in the monograph.

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 anticaries drug products submitted for consideration by the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products. All this information will be put on public display at the office of the Hearing Clerk, Food and Drug Administration, after April 28, 1980, 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 Commissioner 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 no 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.

In the **Federal Register** of January 5, 1972 (37 FR 85), the Commissioner 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 Commissioner published the final regulations providing for the OTC drug review under § 330.10 which were made effective immediately. Pursuant to these regulations, the Commissioner 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 Commissioner 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. Pleinm, 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 meeting are on public display in the office of the Hearing Clerk (HFA-305), Food and Drug Administration (address 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 FDA served: Clarence C. Gilkes, D.D.S., served and 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., served 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.
Herbert 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.
Stanley B. Heifetz, D.D.S., M.P.H.
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.
Phillip 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.
Thomas Schiff, D.D.S.,
Bernard Schneider, D.D.S.,
James H. Stanton
Willard J. Tarbet, D.D.S., Ph.D.
Pactrick Toto, D.D.S.
Aaron Trubman, D.D.S.
Paul Vinton, D.D.S.
A. R. Volpe, 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. FDA reviewed the products previously regarded as drugs and concluded in the **Federal Register** of December 16, 1977 (42 FR 63472) that the following products 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 (BMD). 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 Commissioner 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 BMD. 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 anticaries drug products in this document. The Panel's conclusions and recommendations for oral mucosal injury drug products were published in the **Federal Register** on November 2, 1979 (44 FR 63270) and for drug products for the relief of oral discomfort will be published in a later issue of the **Federal Register.**

In arriving at its conclusions and recommendations, the Panel thoroughly reviewed the literature and data submissions, listened to additional testimony from interested persons, and considered all pertinent data and information submitted through July 13, 1978.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel considered OTC anticaries drug products with respect to the following three categories:

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

Category II. Conditions under which OTC anticaries 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 anticaries drug products.

A. Submissions by Firms—Continued

Firms	Marketed products
Barnangen A.B., Stockholm 12, Sweden.	Vademecum Sugarless Chewing Gum.
Beecham, Inc., Clifton, NJ 07012.	Macleans White Fluoride, Spearmint Flavor.
Carter Products Division, Carter-Wallace, Inc., Canbury, NJ 08512.	Pearl Drops Tooth Polish with Fluoride-Spearmint Flavor, Pearl Drops Tooth Polish with Fluoride-Regular Flavor.
Church and Dwight Co., Inc., Syracuse, NY 13201.	Arm and Hammer Baking Soda, Arm and Hammer Toothpaste.
Janar Co., Grand Rapids, MI 49501.	Janar Iradicav Stannous Fluoride Rinse, Iradicav Fluoride Gel.
Lorvic Corp., Saint Louis, MO 63134.	KARIDIUM Low pH Phosphate Fluoride Topical Gel, KARIDIUM APF (Acidulated Phosphate Fluoride) Topical Gel, KARIDIUM Phosphate-Fluoride Topical Gel, KARIDIUM APF (Acidulated Phosphate Fluoride) Topical Solution, Lorvic Coral II Phosphate-Fluoride Prophylaxis Paste, Lorvic Pink Coral Phosphate-Fluoride Prophylaxis Paste, Lorvic White Coral Phosphate-Fluoride Prophylaxis Paste.
Lever Brothers Co., Edgewater, NJ 07020.	AIM Toothpaaste with Stannous Fluoride Anti-Cavity Ingredient, Silica Dentrifrice with NaMFP.
NDK Co., New Iberia, LA 70560.	NDK Fluoride Dentifrice.
Perident Co., Inc., Oakland, CA 94609.	Perident Salt Toothpaste.
Procter & Gamble Co., Cincinnati, OH 45217.	Crest Toothpaste with Fluoristan Mint Flavor, Crest Toothpaste with Flouristan Regular Flavor, Gleem II Toothpaste.
Sterling Drug, Inc., New York, NY 10016.	Caroid Tooth Powder, Phillips' Tooth Paste.
Warner-Lambert Co., Morris Plains, NJ 07950.	Fluoride Mouthwash (Acidulated Fluoride Phosphate), Fluoride Mouthwash (Stannous Fluoride Effervescent), DiCal Chewing Gum.
Whitehall Laboratories, Inc., New York, NY 10017.	Super-White Kolynos Toothpaste.
In addition, the following firms made related submissions:	
American Pharmaceutical Association, Washington, DC 20037.	Fluoride Dentifrice.
Beecham Products, Inc., Clifton, NJ 07012.	Information on Macleans MFP Toothpaste, Sodium Monofluorophosphate/Calcium Carbonate Dentifrice, Information on Fluoride Dentifrice Expiration Dating, Common Flavor Components and Miscellaneous Formulating Agents, Profile for the In Vitro Efficacy Testing of Macleans MFP Toothpaste, Sodium Monofluorophosphate Safety and Efficacy Data, Information on Macleans Fluoride Toothpaste with 0.76 percent NaMFP in a Calcium Carbonate Base.
Carter Products, Cranbury, NJ 08512.	Dicalcium Phosphate Dihydrate, Sodium Fluoride, Definitions of and Formula Changes for Fluoride Dentifrices, Available Fluoride in Aged Polymethylmethacrylate-Base Dentifrice.
Church and Dwight Co., Inc., Piscataway, NJ 08854.	Comment on Panel Decision to Place Sodium Bicarbonate and All Other Antacids in Category II for Anticaries Activity.

A. Submissions by Firms—Continued

Firms	Marketed products
Colgate-Palmolive Co., Piscataway, NJ 08854.	Reprints of Published Caries Clinical Studies Evaluating Sodium Fluoride Mouthrinses Containing About 0.02 percent F, Literature Reports Concerning Efficacy of Sodium Monofluorophosphate Dentifrices, Summary Information on Sodium Monofluorophosphate Dentifrices, Request for Separate Simplified Guidelines for Sodium Monofluorophosphate Dentifrices, Presentation to the FDA OTC Panel on Dentifrices and Dental Care Agents, Suggested Guidelines for Fluoride Dentifrices, Summary Data Sheet on a Sodium Fluoride, Sodium Bicarbonate Dentifrice, Summary Information on Sodium Fluoride—Sodium Bicarbonate Dentifrices, Analytical Methods for Dentifrices Containing Sodium Monofluorophosphate, Summary of Laboratory Profile, Summary of Silica/MFP Dentifrices, Summary Data Sheet Abrasive/MFP Combinations, Definitions of Formulation Changes for Dental Creams Containing Sodium Monofluorophosphate.
Food and Drug Administration, Rockville, MD 20857.	National Academy of Sciences National Research Council, Drug Efficacy Studies.
Forsyth Dental Center, Boston, MA 02115.	Opinion About the Dentifrice Study Conducted at Tufts University Dental School Under the Supervision of Dr. Helmi Fogels.
Lever Brothers Co., Edgewater, NJ 07020.	Summary of the Laboratory Tests Proposed as Justification for Making Formulation Changes in a Dentifrice Containing 0.4 percent Stannous Fluoride and a Compatible Silica Abrasive, Information on Silica-Based Dentifrice Containing NaMFP, Addendum on Silica-Paste Dentifrices Containing Sodium MFP and Supplement to Lever Stannous Fluoride Submission, Recommendations for the Definitions of Changes in Formulations of Silica Gel Abrasive Dentifrices, Principles of Bioavailability Tests for Fluoride Dentifrices, Supplementary Submission in Support of the Efficacy and Safety of a Dentifrice Comprising 0.76 percent Sodium Monofluorophosphate and a Silica Gel as an Abrasive, Tests for Fluoride Dentifrices, Recommended Laboratory Profile Tests, Submission to OTC Panel on Dentifrice and Dental Care Agents, Clinical Data on a Stannous Fluoride, Silica Based Dentifrice, The Relative Caries Inhibiting Effect of a Stannous Fluoride, Silica Abrasive Dentifrice.
Lorvic Corp., Saint Louis, MO 63134.	Potential Errors in Analyzing Enamel for Fluoride Concentrations and Rates of Acid Dissolution Subsequent to Stannous Fluoride Treatment, Supplement to Submission.
Procter & Gamble Co., Cincinnati, OH 45217.	Establishing Efficacy of Anti-caries Agents and Dentifrices, Laboratory Testing Profile and Quality Assurance Profile for Stannous Fluoride-Calcium Pyrophosphate System (Crest Dentifrice), Laboratory Profiles and the Proposed Expiration Dating for Crest and Gleem II, Formulation Changes in Fluoride Dentifrices, Current Laboratory Profiles and References, Stability of Stannous Fluoride in Dentifrice Formulations and the Effect That Stability Has on Anticaries Efficacy.

A. Submissions by Firms—Continued

Firms	Marketed products
Herbert V. Shuster, Inc., Boston, MA 02122.	SnF_2 Insoluble Sodium Metaphosphate (Toothpaste Methods), Laboratory Profile.
Warner-Lambert Co., Morris Plains, NJ 07950.	Data on Acidulated Fluoride Phosphate Mouthwash (0.02 percent NaF) as a Cariostatic Agent, International Workshop on Fluorides and Dental Caries Reductions, Stannous Fluoride Mouthwash, Specifications and Analytical Data for DiCal Chewing Gum and Dibasic Calcium Phosphate Dihydrate, DiCal Chewing Gum, Supplemental Data Response to FDA Critique, Response to FDA Critique of DiCal Chewing Gum Clinical Studies, Acidulated Fluoride-Phosphate Mouthwash (Sodium Fluoride).
The Proprietary Association, CTFA-PA Dentifrice Task Force, Subgroup on Fluoride Dentifrices, Washington, DC 20006.	Summaries of Laboratory Profile, Standards for Fluoride Dentifrices, Fluoride Dentifrices Joint Submission Clinical and Laboratory Profile, Recommended Laboratory Profile for Fluoride Dentifrices and Presentation to the Panel, Reference Formulations for Performance Standards in the Required Biological Tests of the Fluoride Dentifrice Profiles.
Westwood Research Laboratory, Inc., Westwood, MA 02090.	Testing Procedures for Fluoride Dentifrices.

B. *Ingredients Reviewed by the Panel*

1. *Labeled ingredients contained in marketed products submitted to the Panel.*

Acidulated fluoride phosphate
Alcohol
Benzethonium chloride
Bicarbonate of soda
Calcium phosphate
Calcium pyrophosphate
Cellulose gum
Citric acid
Dicalcium phosphate
Dicalcium phosphate dihydrate
Flavor
Fluoride ion
Glycerin
Glycerol
Gum base (jalaco)
Hydrated silica PFG 32
Hydrogen fluoride
Methylparaben
Milk of magnesia
Mint flavor
Natural flavorings
Orthophosphoric acid
Papain
Phosphate ion
Poloxamer 238
Saccharin
S D Alcohol 38B
Sodium benzoate
Sodium bicarbonate
Sodium carbonate
Sodium citrate
Sodium fluoride
Sodium lauroyl sarcosinate
Sodium lauryl sulfate
Sodium metaphosphate
Sodium monofluorophosphate
Sodium phosphate
Sodium saccharin
Sorbitol
Spearmint flavor
Stannous fluoride
Titanium dioxide
Water

2. *Ingredients contained in marketed products submitted to the Panel but not listed in the labeling of the products.*

Alumina
Alumina (aluminum oxide trihydrate), hydrated
Aluminum hydroxide
Aminoacetic acid
Anethole
Blue color
Buffers
Calcium carbonate (chalk)
Calcium pyrophosphate, high-beta-pphase
Calcium silicate
Caroxymethylcellulose
Carrageenan (sodium and potassium carrageenans)
Carrageenan gum
Carvone
Chewing gum base
Coconut monoglyceride sulfonates
Corn syrup
Dentifrice soap
Dicalcium phosphate anhydrous
Dicalcium phosphate dihydrate
Dicalcium phosphate dihydrate—sugar mix (1:1)
Disodium hydrogen phospate
Flavoring agents
Flavorings, natural
Food, Drug, and Cosmetic coloring agents
Hydrochloric acid
Lathnol LAL
Light mineral oil (food grade)
Magnesium aluminum silicate
Magnesium carbonate
Magnesium hydroxide
Menthol
Oil of peppermint
Phosphoric acid
Pluronic F127
Polak flavor enhancer FOL 650122U
Polyethylene glycol
Polymethylmethacrylate (in the form of small spheres)
Polysorbate 80
Potassium hydroxide
Preciptitated calcium carbonate
Propylene glycol
Pumice
PVP (polyvinyl pyrrolidone)
Red color
Silica
Silica aerogel
Silica gel
Silica gel, dehydrated
Silica, hydrated precipitated
Silica PFG 32, hydrated
Silica xerogel
Silica xerogel, syloid 63
Silicon dioxide
Silicon dioxide (with low aluminum content)
Soap powder
Soduim alkyl sulfate
Sodium alkyl sulfoacetate
Sodium carboxymethylcellulose
Sodium carboxymethylcellulose gum
Sodium dihydrogen phosphate
Sodium dihydrogen phosphate monohydrate
Sodium hydroxide
Sodium metaphosphate, insoluable
Sodium monoglyceride sulfonate
Sodium *N*-lauroyl sarcosinate
Sodium phosphate, dibasic anhydrous reagent
Spice Stannous pyrophosphate
Sugar
Water, distilled
Wintergreen

3. *Other ingredient submitted to and reviewed by the Panel.*

Calcium sucrose phosphate

C. Classification of Ingredients

1. Active ingredients.

Calcium sucrose phosphate
Flouride preparations
Acidulated phosphate fluoride
Sodium flouride
Sodium monofluorophosphate
Stannous fluoride
Dicalcium phosphate dihydrate
Phosphate preparations (providing phosphate ion (PO_4——); not used as inactive ingredient)
Disodium hydrogen phosphate
Phosphoric acid (orthophosphoric acid)
Sodium dihydrogen phosphate
Sodium dihydrogen phosphate monohydrate
Sodium phosphate
Sodium phosphate, dibasic anhydrous reagent
Sodium bicarbonate

2. *Inactive ingredients.* The Panel does not consider this list all inclusive and takes no position as to the value of these ingredients in dental products. The Panel recognizes that the phosphate ingredients and the ingredient sodium bicarbonate are included on both the active and inactive ingredient lists. The Panel has concluded later in this document that the phosphates and sodium bicarbonate are Category II as active ingredients. (See part III paragraph B.2 below—Category II Active Ingredients). The Panel is not opposed to including these phosphate ingredients or sodium bicarbonate in anticaries products as inactive ingredients (buffers, abrasives, etc.) provided anticaries claims are not made for them.

Two of the phosphate ingredients, dicalcium phosphate dihydrate (DCPD) and calcium sucrose phosphate (CaSP), also were submitted to the Panel as additives to sucrose-containing foods. The submissions claimed that these ingredients decreased the cavity-promoting activity of sucrose. During the Panel deliberations the Bureau of Drugs decided that food-additives with noncariogenic claims ("does not promote tooth decay") should properly be reviewed by the Bureau of Foods rather than the Bureau of Drugs because noncariogenic claims are not considered drug claims. Therefore, the Panel has

not addressed noncariogenic claims for these ingredients in this document.

The following ingredients are considered inactive:

Alcohol
Alumina
Alumina (alumina oxide trihydrate), hydrated
Aluminum hydroxide
Aminoacetic acid
Anethole
Benzethonium chloride
Blue color
Buffers
Calcium carbonate (chalk)
Calcium phosphate
Calcium pyrophosphate (calcium pyrophosphate, high-beta-phase)
Calcium silicate
Calcium sucrose phosphate
Carboxymethylcellulose
Carrageenan (sodium and potassium carrageenans)
Carrageenan gum
Carvone
Cellulose gum
Chewing gum
Citric acid
Coconut monoglyceride sulfonates
Coloring agents
Corn syrup
Dentifrice soap
Dicalcium phosphate
Dicalcium phosphate anhydrous
Dicalcium phosphate dihydrate
Dicalcium phosphate dihydrate-sugar mix 1:1
Disodium hydrogen phosphate
Flavoring agents
Flavorings, natural
Glycerin (glycerol)
Gum base
Hydrated silica
Hydrochloric acid
Hydrogen fluoride
Light mineral oil (food grade)
Magnesium aluminum silicate
Magnesium carbonate
Magnesium hydroxide
Menthol
Methylparaben
Milk of magnesia
Mint flavor
Oil of peppermint
Papain
Phosphoric acid (orthophosphoric acid)
Polyethylene glycol
Polymethylmethacrylate (in the form of microspheres)
Polysorbate 80
Potassium hydroxide
Precipitated calcium carbonate
Propylene glycol
Pumice
Red color
Saccharin
S D Alcohol 38B
Silica
Silica gel
Silica gel, dehydrated
Silica, hydrated precipitated
Silicon dioxide
Silicon dioxide (with low aluminum content)
Soap powder
Sodium alkyl sulfate
Sodium alkyl sulfoacetate
Sodium benzoate
Sodium bicarbonate
Sodium carbonate
Sodium carboxymethylcellulose
Sodium carboxymethylcellulose gum
Sodium citrate
Sodium dihydrogen phosphate
Sodium dihydrogen phosphate monohydrate
Sodium hydroxide
Sodium lauryl sulfate
Sodium metaphosphate
Sodium metaphosphate, insoluble
Sodium monoglyceride sulfonate
Sodium *N*-lauroyl sarcosinate
Sodium phosphate, dibasic anhydrous reagent
Sodium saccharin
Sorbitol
Spearmint flavor
Spice
Stannous pyrophosphate
Sugar
Titanium dioxide
Water, distilled
Wintergreen

D. Referenced OTC Volumes

The "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 April 28, 1980, in the office of the Hearing Clerk (HFA–305), Food and Drug Administration, Room 4–65, 5600 Fishers Lane, Rockville, MD 20857.

II. General Statements and Recommendations

A. 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 anticaries drug products. Some of these definitions also apply to the other drug categories reviewed by the Panel. Some degree of variation with other definitions of the same terms may exist.

1. *Abrasion.* Abrasion is the wearing away of tooth substance through some mechanical process. Abrasion usually occurs on the exposed root surfaces of teeth, but under certain circumstances may be seen elsewhere, such as on incisal or proximal surfaces.

2. *Abrasive.* An abrasive is a solid material with the function of cleansing or polishing. Abrasives are important inactive ingredients in anticaries dentifrice formulations and typically comprise up to 50 percent of the total formulation. Abrasives are added to dentifrices to facilitate mechanical removal of dental plaque, debris, and stain from tooth surfaces.

3. *Anticaries agent.* An agent which aids in the prevention of dental caries (decay or cavities).

4. *Antimicrobial agent.* An agent which kills or inhibits the growth and reproduction of micro-organisms.

5. *Binding agent (binder).* As used in dentifrices, a binder is an agent used to prevent the separation of the liquid and solid phases. Binders absorb liquids forming a viscous phase, thus stabilizing the products against separation.

6. *Bioavailability.* The degree to which the drug is absorbed from a dosage form into the body or to its site of action.

7. *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.

8. *Cementum.* The bone-like material covering the root of the tooth. Cementum contains about 45 to 50 percent organic and the balance, inorganic matter. It contains a great number of fibers which attach the tooth to the bone.

9. *Dental calculus.* Mineralized dental plaque accumulates on the tooth surface principally at the gingival margin. One of the major fates of plaque is mineralization. Plaque serves as a matrix for calculus formation. The surface of calculus is usually covered with a nonmineralized layer of plaque. The main irritating feature of calculus is its surface plaque rather than its calcified surface or interior.

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

11. *Dental caries.* A disease of calcified tissues of teeth characterized by demineralization of the inorganic portion and destruction of the organic matrix. Dental caries is thought to not occur without the presence of plaque; however, not all plaques produce caries. The cariogenic plaque, by concentrating acid-forming bacteria at a specific site on a tooth, is responsible for the demineralization of tooth structure; this initiates the first step in dental caries. The bacteria produce acid by anaerobic glycolysis of sugars, mostly sucrose. Plaques vary considerably in their ability to produce acid, depending upon the number and types of acidogenic bacteria present, the availability of sugar, and various other factors.

12. *Dental fluorosis.* Dental fluorosis is a mottling of tooth enamel resulting from imperfect mineralization associated with excessive ingestion of

fluoride during the formation of teeth. Fluorosis appears as discoloration which varies from white spots to brown or even black stains sometimes accompanied by a pitting of the surface. The brown or black stains develop because the poorly calcified surface absorbs colored materials. The frequency and extent of dental fluorosis is chiefly related to the fluoride content of drinking water. The optimum level of fluoride in drinking water for caries prevention is approximately 1 part per million (ppm). At 2 ppm, dental fluorosis is of limited severity and creates no cosmetic problem. Bone (or systemic) fluorosis does not seem to be a problem until levels of 20 to 80 ppm are reached.

13. *Dental gel.* A term used to distinguish a dosage form for delivering an anticaries agent to aid in the prevention of tooth decay. Dental gels are formulated in an anhydrous glycerine base with suitable thickening agents included to adjust viscosity. They do not contain abrasives.

14. *Dental plaque.* A gel-like mat firmly attached to the surface of a tooth or restoration but removable from exposed areas by thorough mechanical cleansing. Plaque formation is normally preceded by deposition of pellicle. (See part II. paragraph B. 29. below—Pellicle.) The gel-like mat is made up of the following:

a. *Microbial masses.* Micro-organisms are the dominant components of mature plaque. The microbial composition of plaque is complex, but, in general, an initial predominance of gram-positive organisms eventually shifts to gram-negative, along with a shift of aerobes to anaerobes.

b. *Intermicrobial matrix.* The matrix is a polysaccharide-protein complex derived from the bacteria, the saliva, and in areas adjacent to the gingival tissues, from gingival fluid. Of the polysaccharides, dextran and levan are the most significant; both are extracellular polysaccharides produced by bacteria. Dextran is the more significant because of its greater quantity and relative insolubility; levan is a much smaller component of the matrix and is used as a carbohydrate nutrient by plaque bacteria in the absence of exogenous sources.

c. *Nonbacterial cellular inclusions.* Both epithelial cells derived from the crevicular epithelium and leukocytes migrating across the crevicular epithelium contribute to plaque formation and structure.

15. *Dental rinse.* A term used to designate a liquid dosage form for rinsing between and around the teeth.

16. *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, flavoring agents, and a finely powdered abrasive as the principal ingredient. In this document a dentifrice is considered to be an abrasive-containing dosage form for delivering anticaries agents to the teeth.

17. *Detergents.* Surface-active ingredients which facilitate the removal of foreign matter from solid surfaces in a solvent (usually water) washing procedure.

18. *Dosage.* A 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 also include the duration of therapy.

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

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

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

22. *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.

23. *Enamel.* The compact and hard substance that covers the crown of the tooth and provides protection for the dentin. The inorganic content of mature enamel amounts to 96–97 percent, by weight, the remainder consisting of organic matter and water.

24. *Erosion.* A loss of tooth substance by a chemical process that does not involve known bacterial action. The smooth lesions, which exhibit no chalkiness, occur most frequently on the labial and buccal surfaces of the teeth.

25. *Fluoride.* The term "fluoride" is used to denote the inorganic forms in which fluorine has combined with other elements. The term "fluoride ion" denotes the negatively charged atom of the chemical element fluorine. The deposition of fluoride in dental enamel has been shown to increase resistance to enamel solubility and therefore dental decay.

26. *Humectant.* A substance, generally a liquid such as glycerin, that is hygroscopic; its presence in a product acts to keep the product moist by attracting water vapor from the surrounding environment.

27. *In vitro.* Within an artificial environment, such as a test tube.

28. *In vivo.* Within the body (animal or human).

29. *Mouthwash (oral rinse).* A solution often containing breath-sweetening, astringent, demulcent, detergent, 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."

30. *Pellicle.* The acquired pellicle is a product of saliva. It is bacteria-free and contains glycoproteins, derivatives of glycoproteins, polypeptides, and lipids. A cleaned tooth surface will form a pellicle within minutes. The formation of this structure is believed to be the first step in plaque formation although not always a necessary prerequisite.

31. *Pharmaceutic aid (nontherapeutic ingredient).* Generally, a substance such as a preservative, antioxidant, solvent, or suspending agent, which in and of itself has little or no therapeutic value but which is useful in the manufacture of suitable dosage forms or which increases the effectiveness or safety of an active agent. Certain drugs with inherent pharmacologic activity of their own may be used to modify the stability, solubility, or toxicity of active agents with which they are formulated; when used in this way, the modifier agent is considered to be a pharmaceutic aid.

32. *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.

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

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

35. *Prophylaxis.* Although "prophylaxis" generally denotes the prevention of disease, this term is also used in dentistry to indicate the removal of plaque and other accumulations on the surfaces of teeth by a dentist or dental hygienist.

36. *Suspending agents.* Those agents that assist in maintaining finely divided solids suspended in a liquid within which they are insoluble and preventing them from flocculating or caking.

37. *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.

B. General Comments

Dental caries is one of the most common diseases of man. While the disease is regarded as multifactorial in nature, the precise etiology is still uncertain. There are, however, certain factors that will influence caries susceptibility both in the pre- and posteruptive periods of tooth development (Ref. 1).

Minerals and trace elements can modify caries susceptibility. The most notable factor is the anticaries effect of fluoride. When this element is ingested, it is incorporated into the hydroxyapatite crystal of developing teeth to form insoluble crystals of fluorapatite. Most of the incorporation is in the enamel surface and less in the deeper layers.

In the posteruptive state, saliva exerts a major influence in protecting teeth from dental caries by exchange of minerals that occur on the enamel surfaces (Ref. 2). Enamel ordinarily resists dissolution when it contains (1) large crystals of hydroxyapatite, (2) fluorapatite, or (3) ions such as tin or lead that can form insoluble compounds (Ref. 3). However, if dissolution occurs, saliva may contribute calcium and phosphate to the tooth surface if the ion concentrations and the pH of saliva are optimal. When fluoride is present in saliva or in plaque, the remineralization process is enhanced (Ref. 4). While fluoride decreases enamel solubility, this action alone does not explain its anticaries action since other ions may reduce enamel solubility but do not reduce dental caries. It is thought that the formation of more stable apatite crystals in the presence of fluoride along with its antienzymatic properties give fluoride its cariostatic effectiveness (Refs. 5 and 6).

Phosphates such as sodium trimetaphosphate and sodium dihydrogen phosphate have been studied for their anticaries activity. The results of these investigations have not been conclusive, and there is some controversy concerning whether their action is local or systemic. Other studies have suggested that there is some interaction between fluoride and phosphate on the enamel surface giving an added cariostatic effect (Ref. 7).

In order for dental caries to occur, three factors are considered necessry (Ref. 8): (1) the teeth must be susceptible to caries; (2) the acid-producing bacteria of the mouth must colonize on the teeth; and (3) a substrate is needed for the bacterial proliferation and production of acids. While the teeth can be made less susceptible to attack by fluorides (Ref. 8) and colonization can be prevented by eliminating dental plaque, the third factor, the necessary substrate, can be at least partially controlled by proper diet. Dental health care personnel have stressed for many years that susceptible individuals should eat a well-balanced diet, which is low in carbohydrates, for prevention of caries (Ref. 9).

Many investigators have implicated sucrose as the major dietary factor in the causation of dental caries, as reviewed by Newbrun (Ref. 10). This source of carbohydrate may be especially harmful to teeth because bacteria can readily use sucrose to produce plaque components (dextrans) and as a source of energy (Ref. 11). Although consideration of sucrose as the major dietary factor in caries production may be an over-simplification (Ref. 12), there is justification for the contention that control of dietary sucrose and other sugars will be helpful in preventing caries (Ref. 13). In spite of this knowledge, and the efforts of dentistry to educate the public, the consumption of sucrose continues to be high in countries with a high standard of living (Refs. 14 and 15).

The Panel is aware of several studies which show high caries incidence when children chew three to five sticks of a sucrose-containing gum each day (Refs. 16, 17, and 18). In some studies, the substitution of sucrose by nonmetabolizable carbohydrates resulted in a significantly lower caries-incidence (Refs. 18 and 19). Candy, cereals, desserts, soft drinks, and many other foods also carry a caries-related substrate source into the mouth; the frequency of eating and the stickiness of the foods are further complicating factors. The Panel therefore makes the following recommendations to the Commissioner:

(1) That all foods which are processed be labeled with their percentage of sucrose and total monosaccharide and disaccharide content. The majority of Panel felt that an FDA study group should determine the lower (safe) limits for these sugars below which the product would be exempt. (A minority of Panel members felt the lower safe limit should be 5 percent for sucrose and 10 percent for total monosacharides and disaccharides.)

(2) That the FDA encourag industry, institutions, organized dentistry, and other interested parties to perform further studies aimed at identifying cariogenic foods.

(3) That industry be encouraged to study food additives which might negate the cariogenic effect of sucrose.

(4) That chewing gums which are proven to have no greater caries-incidence liability than sugarless chewing gums be allowed to make the same "does not promote caries" claim as sugarless chewing gum.

Recommendation (1) should help organized dentistry in diet-control programs for dental-caries prevention. Recommendation (2) may eventually result in warnings placed on dietary constituents which are especially harmful. Recommendation (3) could result in useful anticaries food additives. With reference to recommendation (4), the Panel believes that the evidence at this time is insufficient to allow any gum (on the market or proposed) to make the claim, "does not promote tooth decay."

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C. Drug Misuse and Abuse

The potential for development of drug tolerance and addiction due to the use of dentifrices and dental care agents, even when the patient is on an unsupervised regimen, does not seem to exist. The Panel recognizes that the long history of use of Category I fluoride dentifrices and the Panel's recommended package size limitation for Category I fluoride rinses and gels precludes the need for label warnings on misuse or abuse of these products.

D. Pediatric Considerations

The acute and chronic toxic effects of excessive fluoride ingestion must be considered in determining if anticaries products can be safely used by children. Children are defined by the Panel as persons 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 anticaries drugs the concentration required for children is equal to that needed by adults.

Developing teeth of children under 6 years of age may show objectionable dental fluorosis from repeated ingestion of excessive amounts of fluoride. Epidemiological and clinical findings, however, indicate that the formative state of teeth of children 6 years of age and older (excepting third molars) are too advanced to be affected by excessive daily fluoride ingestion (Refs. 1, 2, and 3). It has also been shown that children 6 years of age have developed control of their swallowing reflex and are able to rinse for 1 minute and expectorate properly (Ref. 4).

A number of studies have been conducted, utilizing a variety of testing procedures, to determine the amount of fluoride ingested during toothbrushing with a fluoride-containing dentrifice (Refs. 5 through 10). These studies indicate that, even in children aged 3 to 6 years, the large majority of individuals swallow less than 0.5 g of toothpaste per brushing and the greatest amount swallowed is only slightly over 1 g. Based on these studies, the Panel concludes that the amount of fluoride swallowed per average brushing can be considered well below a toxic range. Although it is conceivable that a child who regularly swallows excessive amounts of fluoride-containing toothpaste and also consumes fluoridated water could have a total daily fluoride intake in the range that produces dental fluorosis, there is a lack of any documentation that dental fluorosis has increased significantly following extremely widespread use of fluoride-containing dentrifices for approximately 15 years.

In view of these considerations the Panel recommends that fluoride dental rinses and gels be labeled for use by adults and children 6 years of age and older. Also, the Panel recommends that fluoride dentifrices be labeled for use by adults and children 2 years of age and older. Fluoride dentifrices should also be labeled to indicate that children under 6 years of age should be supervised in the use of fluoride dentifrices.

The Panel is aware of the concerns of acute toxicity from excessive fluoride ingestion, e.g., if a child were to ingest the entire contents of a fluoride-containing product. In 1958, the Council on Dental Therapeutics of the American Dental Association (ADA) first recommended that no more than 120 mg of fluorine should be dispensed at any one time. Such an amount represents a reasonable safety factor to be applied to a dental rinse which is packaged in a single container (Ref. 11). Experience during the past 20 years has borne out the safety of the Council's precautionary limit of fluoride.

The Panel concurs with the ADA recommendations on package-size limitations with respect to dental rinses and recommends that the package size of dental gels also be limited to 120 mg fluorine. In addition, the Panel recommends that dentifrice (abrasive-containing) preparations should be limited to 260 mg fluorine. The Panel is aware that this is the largest amount that has been approved by the FDA for this type of product.

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E. Principles Applicable to Combination Policy

The Panel recognizes that there may be a reason for combining active ingredients in certain OTC drugs; however, such combinations must be based on a sound and logical scientific rationale. In the case of OTC anticaries drug products, the Panel does not believe that there are any combinations of active ingredients that are presently marketed that it wishes to recognize as rational and beneficial for OTC use.

The Panel is aware of some data which indicate that certain antimicrobial agents have been shown to reduce markedly bacterial

accumulations on the teeth, and, thus, it might be argued have some promise in reducing caries. At this time, however, the Panel feels that the data supporting an effect are preliminary and are an inadequate basis for forming any conclusions.

Accordingly, the Panel has concluded that any combination of an OTC anticaries drug product and an antimicrobial agent or an antiseptic agent be classified in Category II.

The effectiveness of combining two or more fluorides has not been tested. The Panel recognizes that sodium monofluorophosphate exists in water in dynamic equilibrium with sodium fluoride, and with the various ions produced by the hydrolysis of the compound. This reaction, however, should not be interpreted as producing a combination drug product. The Panel has elected to consider the sodium monofluorophosphate compound as a single active ingredient, even though it is aware that that compound always contains small amounts of sodium fluoride. The hydrolysis does not affect either the safety or the effectiveness of the formulation of sodium monofluorophosphate.

The Panel considers it appropriate to restrict OTC anticaries drug products to single active ingredients because only single active ingredient products have undergone substantial clinical and laboratory testing.

Any company wishing to market an OTC combination drug product for the prevention and reduction of dental caries will have to obtain an approved new drug application (NDA) prior to marketing.

F. Inactive Ingredients

The Panel is aware of the need for the inclusion of inactive ingredients in OTC anticaries drug products. Preferably, these should be limited to agents that are considered necessary such as abrasives, preservatives, aromatics, vehicles, colorants, sweeteners, anti-oxidants, buffers, and agents required for particular dosage forms.

The Panel did not undertake an extensive review of inactive ingredients, because it is the view of this 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 dentifrices and dental care agents except for abrasives. The effects of abrasives in anticaries drug products are discussed elsewhere in this document. (See part III. paragraph A.2. below—Fluoride dentifrices.)

The Panel recommends that in view of the inactive ingredients, such as sodium lauryl sarcosinate, which have caused oral mucosal irritation, the final formulation of OTC anticaries drug products should be shown to be safe and nonirritating. Monitoring of consumer complaints should detect, at an early stage, irritation or allergic manifestations not detectable in animal studies.

G. Labeling for OTC Anticaries Drug Products

The Panel reviewed and concurs with the FDA's OTC drug labeling regulations (21 CFR 201.61(a), (b), and (c) and 21 CFR 330.10 (a)(4)(v)).

Having reviewed all of the labels of OTC anticaries drug products submitted, the Panel recommends that labeling include the following:

1. *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 name and 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 when possible.

The labeling must indicate the principal intended action of the active 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.

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 all inactive ingredients be listed on the label in descending order of quantity. 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 cosmetic products (21 CFR 701.3).

2. *Indications.* The indications for use of a dentifrice, dental rinse, or dental gel should be simply and clearly stated and should provide the user with a reasonable expectation of results to be anticipated from use of the product.

Statements of indications for use should be specific and confined to the conditions for which the product is recommended. Thus, a prominent and conspicuous statement must be made of general pharmacotherapeutic action. For example, anticaries drug products should be labeled to indicate their usage, i.e., "Aids in the prevention of dental caries (decay or cavities)."

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

The label should include a clear statement of the usually effective minimum and, where applicable, maximum doses (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. The Panel will recommend specific directions for use under each drug statement in later sections of this document.

4. *Warnings.* Labeling of dental care products should include warnings against unsafe use, side effects, and adverse reactions. The Panel recognizes that the long history of safe use of fluoride dentifrices precludes the need for any such warnings on the label.

However, the Panel considers the following warning necessary for the safe use of fluoride rinses and gels: "Do not swallow. Developing teeth of children under 6 years of age may become permanently discolored if excessive amounts of fluoride are repeatedly swallowed."

5. *Other statements on the label.* In addition to the warning statements above for dental rinses and gels, the following statements should appear on the label of fluoride dental rinses and gels:

a. *For all dental rinses and gels.* "This is not a dentifrice."

b. *For stannous fluoride dental rinses and gels.* "This product may produce surface staining of the teeth. Adequate tooth brushing may prevent these stains which are not harmful or permanent and may be removed by your dentist."

6. *Other allowable statements for dentifrices.* The labeling may also include, where the product has been approved by ADA, the statement: "(Product name) has been shown to be an effective decay-preventive dentifrice that can be of significant value when used in a conscientiously applied

program of oral hygiene and regular professional care."

7. *Packaging.* The Panel recommends that fluoride dental rinses and gels be packaged in containers with safety closures. The packaging of fluoride dental rinses should provide a means for measuring the dosage, or the product should be marketed in single dose containers. Limitation of package size is recommended for all anticaries products in view of safety considerations discussed previously in this document. (See part II. paragraph D. above—Pediatric Considerations.)

H. *General Statements on the Determination of Safety and Effectiveness for OTC Anticaries Drug Products*

The Panel evaluated the safety and effectiveness of OTC anticaries active ingredients, as well as 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 possibility that the drug might cause adverse effects on teeth or irritation of the oral mucosa was evaluated. Animal studies were 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.

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, the Panel considered separately each pharmacotherapeutic group under review although certain general principles apply to all groups.

In terms of effectiveness, animal anticaries studies are helpful because certain animal models 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. Clinical experience of a general nature, if documented by qualified experts, added somewhat to the final decision.

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. The effectiveness of such products may never have been subjected to scientific investigation 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.

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 nor substitute for the Panel's other sources of knowledge of safety, effectiveness, and rationale for such products.

III. Anticaries Agents for OTC Drug Use

A. General Discussion

1. *Fluorides.* Inorganic fluorides supply the teeth with fluoride ion, which has been shown to be effective in helping to prevent dental caries as reviewed by Horowitz (Ref. 1). Fluoride has been safely added to the drinking water as a public health measure, and other methods of fluoride administration are also beneficial in helping to prevent dental caries (Refs. 1 through 6). For example, dentists have used topical, in-office fluoride treatment to provide anticaries benefits (Ref. 6). However, not everyone in the United States consumes fluoridated water nor are they able to receive professional fluoride treatments. Even if the populace had either form of fluoride application, many studies have shown that further supplementation of fluoride by means of rinses, dentifrices, and other modes of application would offer additional protection (Refs. 2 through 6). When there is deficient systemic intake of fluorides and consumers are not receiving topical fluoride treatments in dental offices, the Panel recommends that fluoride rinses or fluoride dentifrices to be used to reduce caries.

One of the major advances in OTC dental drugs was the addition of fluorides to dentifrices. The first prophylactic dentifrice to gain acceptance by FDA and the ADA was a stannous fluoride dentifrice introduced in 1955. A major factor in the development of this dentifrice was the introduction of a new abrasive which minimized inactivation of the fluoride. The ADA Council on Dental Therapeutics classified this dentifrice Group B (provisional) in 1960 and Group A (accepted) in 1964, allowing the use of its Seal of Acceptance on the label. This action was a great stimulus to the development of other fluoride dentifrices with compatible abrasives. Three additional stannous fluoride dentifrices received Group B ratings from the ADA, but none of the latter three are presently on the market.

A dentifrice containing sodium monofluorophosphate (Na MFP) achieved Group A acceptance by the ADA in 1969 after having obtained an effective NDA from FDA in 1967.

Sodium fluoride was considered a potentially active ingredient for anticaries dentifrices because it was effective in topical fluoride treatments in dental offices. Results of early tests of sodium fluoride dentifrices were disappointing, however, because the availability of the active ingredient, fluoride, was decreased by interaction with the abrasives used. Following the development of a more compatible abrasive for use with stannous fluoride, a dentifrice formulation of sodium fluoride with a similar type of abrasive showed effectiveness in several clinical studies. The sodium fluoride dentifrice was submitted to FDA through NDA procedures and approved for marketing by the agency on October 29, 1973.

In Sweden, Torell and his colleagues in the early 1960's evaluated various dosage forms for application of fluoride to the teeth (Ref. 7). They found that of the regimens tested, effectiveness in descending order of effectiveness for caries reduction was provided by (1) sodium fluoride rinse once daily, (2) sodium fluoride rinse fortnightly, (3)

stannous fluoride dentifrice, (4) sodium fluoride topical treatment (professional application), (5) sodium fluoride bicarbonate dentifrice, and (6) stannous fluoride topical treatment (professional application). The daily sodium fluoride rinse showed greater effectiveness in controlling dental caries than any of the other regimens. Differences between the two fluoride dentifrices were not statistically significant. In a separate study, these authors reported effectiveness of a monofluorophosphate-calcium carbonate dentifrice system.

Further studies verifying the Swedish observations as well as additional investigations on other modes of fluoride delivery led the FDA Dental Drug Products Advisory Committee to recommend to the Commissioner approval of seven types of topical fluoride preparations as prescription drugs or for professional use. The Commissioner accepted the recommendation and these formulations were published in the **Federal Register** of May 14 (39 FR 17245), June 26 (39 FR 23081), and November 7, 1974 (39 FR 39488).

The Dental Drug Products Advisory Committee also recommended to the Advisory Review Panel on OTC Dentifrice and Dental Care Agent Drug Products that the neutral and acidulated sodium fluoride solutions intended for daily use would be good candidates for over-the-counter drug status (39 FR 17245). This opinion was taken under advisement by the Panel and was helpful in the deliberations on fluoride dental rinses.

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2. *Abrasives.* Abrasives are important ingredients of dentifrice formuations and typically comprise up to 50 percent of the total formulation. Consideration of abraisives is essential because of the potential for active ingredient/abrasive incompatibility resulting in a decrease in the effectiveness of the active ingredient.

The cleansing function of a dentifrice is achieved by the mechanical removal of dental plaque, stain, and debris from tooth surfaces by the abrasive system. This function relies upon the difference in hardness between surface debris and the tooth. This hardness differential between debris and the enamel of the tooth crown is large; thus there is little concern about the use of abrasives that can safely achieve through cleansing of the enamel tooth crown. However, the root portion of the tooth is composed of a thin layer of cementum over dentin. Enamel is about 10 to 20 times as hard as this root portion. If the root portion of the tooth is exposed by gingival recession and is brushed with abrasives, potential exists for mechanical removal of tooth substance.

The exact contribution of dentifrice abrasives to mechanical removal of tooth substance from root surfaces and restorative materials of comparable hardness, such as the acrylics, is unknown. Theoretically at least, the abrasivity level of the dentifrice, the nature of the toothbrush, and the technique used in brushing the teeth could contribute to a clinical effect. Proper toothbrushing technique is believed to minimize the possibility for mechanical removal of tooth substance and restorative materials.

The common major abrasive systems used in dentifrices are alumina, dicalcium phosphate (dihydrate and anhydrous), chalk, insoluble sodium metaphosphate (IMP), calcium pyrophosphate, and silicas. Dicalcium phosphate dihydrate has a relatively low level of abrasivity whereas the anhydrous compound has a considerably higher level. Blends of the two compounds can be and are used to achieve abrasivity levels between the two single entities. Similarly, a number of silicas, differing in particle sized and hardness, are available. As with the dicalcium phosphates, silicas can be used singly or in mixtures to achieve a specific level of abrasivity. The same is true with chalks that are available from a number of sources and can differ substantially in abrasivity characteristics. Calcium pyrophosphate and insoluble sodium metaphosphate (IMP) each have a fairly narrow range of abrasivity; however, the manufacture and method of processing can alter somewhat the abrasivity level. The heat processing of dicalcium phosphate dihydrate converts the crystalline structure into calcium pyrophosphate, which may have one or more of three phases: the alpha phase is most abrasive, beta is intermediate, and the gamma phase is least abrasive. A mixture containing high-beta-phase, about 80 percent, and the rest gamma phase, has been shown to have useful properties for fluoride dentifrices. The beta phase of calcium pyrophsophate has a lower level of ionizable calcium. The lower level of ionaizable calcium results in more fluoride ion being available for effectiveness.

There are a number of other abrasives that could be used in dentifrices providing that studies establish safety at the concentrations used in dentifrices. Some of these are now used outside the United States and others are either minor constituents in present formulations or are still in the developmental stages. Examples of these are the acrylics, aluminum oxide, zirconium silicate, aluminum silicate, and other mineral clays.

In the evaluation of the abrasivity of a dentifrice, it is important to conduct tests on the complete formulation. The abrasivity level of the dentifrice is the result of the interaction between the various ingredients and is not merely reflective of the abrasive compound and its concentration in the formula.

The abrasivity of the dentifrice per se can be measured in the laboratory very precisely but the abrasivity achieved in actual use depends upon toothbrushing, as well as a number of factors mentioned earlier including method of toothbrushing, actual load placed on the brush, duration of brushing, and toothbrush characteristics (Ref. 1). In the opinion of the Panel, there is no indication for a dentifrice for daily use with an abrasivity level above 250 as measured by a method using dentin as a substrate (Ref. 1). A higher level of abrasivity would mean additional risk without a substantial increase in benefit.

The clinical cleansing capability of dentifrices has shown one positive linear correlation with laboratory abrasivity data using dentin as a substrate and laboratory dicalcium phosphate dentifrices formulated to represent the general abrasivity range

availabe for commercial dentifrices in the United States (Ref. 2). Somewhat comparable information has been obtained for chalk-based dentifrices (Ref. 3). It may not be possible to extrapolate from clinical and laboratory data on one abrasive system to all other systems, but in general the correlation seems reasonable. There may be examples where there is no correlation between laboratory abrasivity and either laboratory cleansing data or clinical cleansing results.

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(3) Davis, W. B., P. M. Dean, and J. Winchester, "Cleaning Power and Dentine Abrasivity Relationship of Calcium Carbonate Toothpastes," *Journal of Dental Research*, 56:A67, 1977.

3. *Floride dentifrices.* The Panel is aware that consumers may be easily misled by the promise that a particular anticaries preparation will prevent or reduce dental caries, because the effectiveness of the anticaries product is not self-evident in the same sense, for example, as the easily recognizable effectiveness of aspirin in relieving pain. In the Panel's view, it is hardly possible for an individual consumer to determine the benefits of using a product containing an anticaries agent such as flouoride. This is of particular concern to the Panel because results of early clinical studies to demonstrate the effectiveness of flouride-containing dentifrices were generally less impressive than expected (Ref. 1). A number of reasons may be responsible for these results. The nature of the clinical caries trial is such that, unless conducted with a high level of expertise employing appropriate criteria, the results can be inconclusive. However, a major part of the problem was related to incompatibility of the fluoride ion with the abrasive used in the dentifrice. Studies were initiated to increase the compatibility between the fluoride and the abrasive system and to formulate products which would deliver or release the fluoride to the teeth.

Calcium pyrophosphate was developed as a dentifrice abrasive which could be combined with stannous fluoride (Ref. 2), and later high-beta-phase clacium pyrophosphate was used successfully with sodium fluoride (Ref. 3). Dental scientists then conducted many clinical studies (Ref. 4) with these fluoride-abrasive combination systems to show that they were effective in reducing human dental caries in a variety of circumstances. Because of the early failures of certain fluoride toothpaste formulations to reduce the incidence of caries, the dental profession was unwilling to accept formulation changes without clinical demonstration of effectiveness. As more and more fluoride dentifrices, including sodium monofluorophosphate dentifrices, showed effectiveness in clinical studies, it became apparent that the availability of the fluoride was one measure of an effective fluoride dentifrice formulation.

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4. *Laboratory testing profiles.* The Panel concludes that all of the fluoride compounds placed in Category I as active ingredients have been shown through numerous clinical trials to be safe and effective for OTC use. However, because the abrasive in dentifrice formulations may alter the availability of the fluoride to the teeth, the Panel concludes that certain stability and bioequivalency data on the final formulation are necessary before that formulation is marketed.

In the opinion of the Panel, the extensive amount of testing, which has included laboratory, animal, and clinical tests, allows prediction as to which dentifrice formulations will be effective. The Panel concludes that, if certain analytic and biologic tests are conducted and acceptable test values are achieved, clinical testing is not required. The acceptable test values are those obtained from dentifrice formulations that have already been proven to be effective through clinical testing. The acceptable values for each of the Category I active ingredients are summarized in the tables below. The methodology for conducting these tests is included in a submission to the Panel (Ref. 1). Manufacturers must keep on file a "Laboratory Testing Profile" (the values obtained from the analytic and biologic testing) for each dentifrice formulation and on any reformulated product with the same abrasive system.

If at any time a Category I dentifrice formulation does not meet the laboratory testing values equal to or greater than the highest fluoride values listed in the tables below, but it has been shown to be clinically effective, the manufacturer can petition FDA to amend the monograph to include that formulation.

If a manufacturer wishes to use an untested chemical compound as a fluoride source, he or she must file to obtain an approved NDA in accordance with FDA's new drug regulations.

If the manufacturer wishes to use a new abrasive with a Category I fluoride, the product will be in Category I provided that the new abrasive is safe and that the new formulation has laboratory testing values equal to or greater than the highest fluoride values listed in the tables below for that same fluoride compound. The Panel recommends that safety for any new abrasive should be established according to current regulations for inactive ingredients (21 CFR 210.3(d) and 330.1(e)) and to the Panel's specifications for abrasivity. (See part III. paragraph A.3. above—Fluoride dentifrices.)

The Panel recommends that expiration dates be included on the cartons of dentifrice products. The analytic and biologic test values for aged products should be used by the manufacturer to determine an expiration date for his product. Each manufacturer should have data on record which indicate that its product meets the aged minimal values for these tests at the time of expiration. Also, the expiration date should conform to good manufacturing practice to take into account other elements and properties of the formulation.

The following analytical test values apply to all Category I fluoride abrasive-containing dentifrices:

1. Theoretical total fluorine: 1,000 ppm (allowable range 900–1,100 ppm).
2. Specific gravity: 1.3 to 1.7.

All Category I fluoride dentifrices must meet the test requirements of any two of the following biological tests:

1. Enamel solubility reduction.
2. Fluoride uptake by enamel.
3. Animal caries reduction.

The performance standard which must be met for these biological tests for both fresh and aged minimal values obtained for the dentifrice formulations requires that the numerical score in the biological test shall be both (1) significantly different from the score for a placebo formulation, and (2) no lower

than the score for the reference formulation at the 90-percent confidence level. The reference formulations to be used in the above biological tests are described in a submission to the Panel (Ref. 2). Any clinically effective sodium monofluorophosphate/abrasive formulation can be used as the performance standard for any other sodium monofluorophosphate/abrasive formulation.

The analytical test values in the following tables apply to the indicated Category I fluoride dentifrices:

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TABLE 1--ACCEPTABLE TEST VALUES FOR SODIUM FLUORIDE DENTIFRICES

I. Soluble Fluoride Ion (F^-)

Abrasive	Fresh F^- value[1/]	Aged minimal F^- Value[1/]	Maximum test dilution (w/w)
High-beta-phase calcium pyrophosphate	648 ppm	403 ppm	1:10

II. Hydrogen Ion Concentration (pH)

Abrasive	Test value	Maximum test dilution (w/w)
High-beta-phase calcium pyrophosphate	6.5-8.0	1:10

[1/]Values listed are parts of the measured substance per million parts of the whole dentifrice.

TABLE 2--ACCEPTABLE TEST VALUES FOR SODIUM MONOFLUOROPHOSPHATE DENTIFRICES

I. Soluble Fluoride Ions ($PO_3F^=$ and F^-)[1/]

Abrasive	Ion	Fresh value[2/]	Aged minimal value[2/]	Maximum test dilution (w/w)
Applicable to all abrasives	$PO_3F^=$	650 ppm[3/]	Half total ($PO_3F^=$ and F^-) value	1:10
	F^-	10-150 ppm	10 ppm to $PO_3F^=$ value	1:10
	Total ($PO_3F^=$ and F^-)	800 ppm	600 ppm	1:10

II. Hydrogen Ion Concentration (pH)

Abrasive	Test value	Maximum test dilution (w/w)
Alumina	5.0-9.0	1:10
Calcium carbonate	7.0-10.0	1:10
Calcium pyrophosphate	5.0-5.4	1:10
Dicalcium phosphate	6.5-7.8	1:10
Insoluble sodium metaphosphate	5.6-6.9	1:10
Silica	5.5-7.4	1:10

1/For the compound sodium monofluorophosphate in a dentifrice formulation, fluoride ion exists as a combination of the ions $PO_3F^=$ and F^-. Values are given for each of these ions as well as the "Total": combination of $PO_3F^=$ plus F^-.

2/Values listed are parts of the measured substance per million parts of the whole dentifrice.

3/Soluble $PO_3F^=$ is derived either by direct analytic measurement, or by subtracting soluble fluoride ion (F^-) from total soluble available fluorine ($PO_3F^=$ plus F^-).

TABLE 3--ACCEPTABLE TEST VALUES FOR STANNOUS FLUORIDE DENTIFRICES

I. Soluble Fluoride Ion (F^-)

Abrasive	Fresh F^- value[1]	Aged minimal F^- value[1]	Maximum test dilution (w/w)
Insoluble sodium metaphosphate, silica, and others	600 ppm	500 ppm	1:10
Calcium pyrophosphate	288 ppm	108 ppm[2]	1:10

II. Soluble Stannous Ion (Sn^{++})

Abrasive	Fresh Sn^{++} value[1]	Aged minimal Sn^{++} value[1]	Maximum test dilution (w/w)
Insoluble sodium metaphosphate	2,000 ppm	Qualitatively detectable	1:10
Silica and others	Qualitatively detectable	Qualitatively detectable	1:10
Calcium pyrophosphate	900 ppm	Qualitatively detectable	1:10

III. Hydrogen Ion Concentration (pH)

Abrasive	Test value	Maximum test dilution (w/w)
Insoluble sodium metaphosphate	4.2-5.4	1:10
Silica	4.6-5.1	1:10
Calcium pyrophosphate	4.4-5.1	1:10

[1]/Values listed are parts of the measured substance per million parts of the whole dentifrice.

[2]/Value corresponds to that of aged product found clinically effective.

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References

(1) OTC Volume 080248.
(2) OTC Volume 080253.

5. *Fluoride rinses.* The caries-inhibiting effect of frequent mouth rinsing with dilute fluoride solutions has been evaluated in more than 20 large-scale clinical trials (Refs. 1 and 2). Discussions of these trials are included later in this document. Most of these studies were conducted in nonfluoridated communities and used sodium fluoride, either in neutral or acidulated phosphate form, as the active rinse ingredient. Essentially all the studies have reported inhibition of incremental dental caries, the benefits ranging from 20 to 50 percent.

The safety and effectiveness of frequent rinsing with dilute fluoride solutions in the control of dental caries is generally recognized (Refs. 1 and 3). In addition, the FDA Dental Drug Products Advisory Committee has recommended that consideration should be given to designating certain fluoride rinses as OTC dental drug products.

The laboratory testing of fresh and aged products must certify that the measured amount of fluoride ion represents the total theoretical amount of fluorine present as formulated in the product plus or minus 10 percent. The expiration date can be based on this certification and on good manufacturing practice regulations.

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6. *Fluoride gel.* Four studies on stannous fluoride dental gels containing 0.4 percent stannous fluoride in anhydrous glycerin have been published (Refs. 1 through 4). These studies provide reasonable documentation of effectiveness of the dental gel dosage form. The Panel, therefore, concludes that 0.4 percent stannous fluoride dental gel is effective as an anticaries agent.

The laboratory testing of fresh and aged products must certify that the measured amount of fluoride ion represents the total theoretical amount of fluorine present as formulated in the product plus or minus 10 percent. The expiration date can be based on this certification and good manufacturing practice regulations.

The Panel recommended that these products be used in addition to rather than as a substitute for a dentifrice.

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B. Categorization of Data

1. *Category I conditions under which anticaries ingredients 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

Sodium fluoride (dentifrice)
Sodium monofluorophosphate (dentifrice)
Stannous fluoride (dentifrice)
Acidulated phosphate fluoride (rinse)
Sodium fluoride (rinse)
Stannous fluoride (rinse)
Stannous fluoride (gel)

a. *Sodium fluoride (dentifrice).* The Panel concludes that 0.22 percent sodium fluoride with a compatible abrasive in a dentifrice product is safe and effective for OTC use as an anticaries agent when marketed in packages containing not more than 260 mg of fluorine.

(1) *Safety.* The toxicity of fluoride compounds can be attributed to the fluoride ion, which is considered to be a protoplasmic poison. Study of the recorded cases of acute fluoride poisonings indicate that a dose range of 5 to 10 g of sodium fluoride can be considered a lethal dose for a 70 kg man (Ref. 1).

Much is known of the chronic effects of fluoride because of the widespread use of dietary fluoride in drinking water to provide protection against dental caries. Presently, more than 105 million people in the United States live in areas in which the water supplies contain 0.7 ppm or more fluoride ion, with 94 million of these people receiving water supplemented with additional fluoride to provide a trace level of approximately 1 ppm (Ref. 2). Drinking water having a level of approximately 1 ppm of fluoride will provide a substantial reduction of about 60 percent in the incidence of dental decay without any adverse effect. Dental fluorosis has been reported from daily intake of water with 2 to 10 ppm of fluoride and crippling skeletal fluorosis with levels of 20 to 80 ppm of fluoride in the drinking water (Ref. 3). It should be noted that dental fluorosis occurs only when excessive fluorides are ingested regularly during the period of tooth development.

A number of studies have been conducted, utilizing a variety of testing procedures, to determine the fluoride ingested during toothbrushing with a fluoride-containing dentifrice (Refs. 4 through 9). These studies indicate that, even in children aged 3 to 6 years, the large majority of individuals swallow less than 0.5 g of toothpaste per brushing. The greatest amount swallowed was reported by Hargreaves et al. (Ref. 8) as being only slightly over 1 g. If the above information is used when considering a toothpaste formulation containing 0.22 percent sodium fluoride, the amount of fluoride swallowed per average brushing would be 0.25 mg or less. Studies by Ericsson (Ref. 6), Duckworth and Joyston-Bechal (Ref. 10), Barnhart (Ref. 11), and Glass et al. (Ref. 9) all showed the amount swallowed was substantially less than that shown by Hargreaves et al. (Refs. 4 and 8). This amount can be considered well below a toxic range.

Although it is conceivable that a child who regularly swallows excessive amounts of fluoride-containing toothpaste and also consumes fluoridated water could have a total daily fluoride intake in the range that produces dental fluorosis, there is a lack of any documentation that dental fluorosis has increased significantly following extremely widespread use of fluoride-containing dentifrices for approximately 15 years.

(2) *Effectiveness.* The data from six clinical trials utilizing a dentifrice containing 0.22 percent sodium fluoride with a 40-percent high-beta-phase calcium pyrophosphate abrasive system indicate a statistically significant caries

reduction at a 95-percent confidence level (Refs. 12 through 16). These studies all employed a nonfluoride control and varied from 16 months to 36 months in duration. In only one of the studies one of the investigators did not find a reduction in caries that was statistically significant at the 95-percent confidence level. These clinical studies permit the Panel to conclude that sodium fluoride with this abrasive combination in a dentifrice is effective in the prevention of dental caries.

(3) *Dosage.* Adults and children 2 years of age and older, brush teeth thoroughly at least once daily with 0.22 percent sodium fluoride in a suitable dentifrice formulation.

(4) *Labeling.* The Panel recommends the Category I labeling. (See part III. paragraph B.1. below—Category I Labeling.)

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(14) Reed, M. W., "Clinical Evaluation of Three Concentrations of Sodium Fluoride in Dentifrices," *Journal of the American Dental Association,* 87:1401-1403, 1973.

(15) OTC Volume 080099.

(16) Reed, M. W., and J. D. King, "A Clinical Evaluation of a Sodium Fluoride Dentifrice," *Pharmacology and Therapeutics in Dentistry,* 2:77-82, 1975.

(b) *Sodium monofluorophosphate (dentifrice).* The Panel concludes that 0.76 percent sodium monofluorophosphate (NaMFP) with a compatible abrasive in a dentifrice product is safe and effective for OTC use as an anticaries agent when marketed in packages containing not more than 260 mg of fluorine.

(1) *Safety.* The toxicity of fluoride and the ingestion of fluoride during toothbrushing has been discussed previously. (See part III. paragraph B.1.a.(1) above—Safety.) Acute and subacute toxicity studies with sodium monofluorophosphate suggest that the compound on the basis of both milligrams of compound and milligrams of fluorine is less toxic than sodium fluoride (Refs. 1, 2, and 3). Although the accumulation of fluoride in bone and teeth appears to be similar for sodium monofluorophosphate and sodium fluoride when used at the same fluoride concentration (Ref. 4), studies with radioactive fluoride suggest that the lower toxicity may result from the gradual release of the fluoride ions from the monofluorophosphate (Ref. 5).

Animal feeding studies suggest that the chronic toxicity of sodium monofluorophosphate and sodium fluoride are of the same order and have similar characteristics with the kidney being the most susceptible to pathological change (Ref. 6). Further, the two compounds seem to produce the same degree of mottling in the incisors of albino rats (Ref. 7). When the same quantities of fluoride are given to rats in the form of sodium fluoride, sodium monofluorophosphate, stannous fluoride, and stannous chlorofluoride, similar amounts of fluorine are found in the skeleton (Ref. 8). The monofluorophosphate ion ($PO_3F^=$) also does not appear to pass the placenta to any greater extent than the fluoride ion (Ref. 9).

There is no available information on human toxicity with sodium monofluorophosphate as there is with sodium fluoride. Although acute toxicity of sodium monofluorophosphate in animals is less than that of sodium fluoride, the chronic toxicity is similar. It would, therefore, appear suitable to consider, for human use, that the two compounds have similar toxicity in terms of the fluorine present.

(2) *Effectiveness.* The effectiveness of a 0.76-percent sodium monofluorophosphate toothpaste in reducing the incidence of dental decay has been established by a number of clinical trials under varying test conditions and with different abrasive systems.

Fanning et al. (Ref. 10) conducted a double-blind unsupervised study with a 0.76-percent sodium monofluorophosphate toothpaste with a compatible base of insoluble sodium metaphosphate as the abrasive. When compared to the control, the use of the dentifrice resulted in approximately 21 percent fewer new decayed surfaces over the 2-year period ($P = 0.001$).

Mergele (Refs. 11 and 12) conducted two clinical trials with 0.76-percent sodium monofluorophosphate dentifrice formulations. In the one conducted among three groups of handicapped subjects residing in state institutions where the water did not contain any significant amounts of fluoride, the investigators found that after 22 months of supervised toothbrushing the test group experienced a lower incidence of new caries than the group using the control paste (Ref. 11). The difference compared with the control was significant in all indices of new caries measurement and amounted to a 21-percent reduction in the most commonly used index, the net new, decayed, missing, and filled surfaces (DMFS) index.

In the second trial conducted by Mergele (Ref. 12), using a similar 0.76-percent sodium monofluorophosphate dentifrice formulation, conducted where the local water supply contained about 1 ppm of fluoride, children in the fifth through eighth grades attending public schools were used as subjects. All the toothbrushing was performed in the homes of the subjects, unsupervised. The test subjects were found to have a lower DMFS index than the control paste in 3 years of unsupervised brushing. The difference compared with the control dentifrice was significant at the 95-percent level of confidence.

Thomas and Jamison (Ref. 13) ran a 2-year clinical study in six homes for children in an area in which the water did not contain an appreciable concentration of fluoride ions. Children from 8 to 16 years of age were assigned randomly to use a control dentifrice or one of two experimental dentifrices,

under supervision, at least twice daily. Both of the experimental dentifrices contained 0.76 percent sodium monofluorophosphate; one formulation had only 1 percent sodium *N*-lauroyl sarcosinate, whereas the other contained 2 percent of that compound. All three dentifrices contained insoluble sodium metaphosphate as the compatible abrasive. After 22.5 months the incidence of caries was statistically significantly lower in the children who used the experimental dentifrices than in the children who used the control toothpaste. The rates of incidence of dental caries were comparable for the children who used the two experimental dentifrices. The estimates of effectiveness of the monofluorophosphate dentifrices which contained 1 and 2 percent sodium *N*-lauroyl sarcosinate were 31 percent and 29 percent for decayed filled teeth (DFT) and decayed filled surfaces (DFS), respectively. Based on DFS data, both test groups had approximately 29 percent fewer lesions than the control group.

Abrasive systems other than insoluble sodium metaphosphate have been tested with sodium monofluorophosphate. Naylor and Emslie (Ref. 14) conducted a double-blind, controlled clinical trial of 3 years duration. Eleven- and 12-year-old British school children tested the effectiveness of a toothpaste containing 0.76 percent sodium monofluorophosphate with dicalcium phosphate dihydrate as the principal abrasive agent. The results showed that the experimental paste produced significant reductions in caries experience as compared with the control paste. The reductions were greatest in respect to new carious surfaces on teeth which erupted during the study.

Andlaw and Tucker (Ref. 15) tested a dentifrice containing 0.8 percent sodium monofluorophosphate and employing aluminum oxide trihydrate as the abrasive. This study utilized British school children 11 to 12 years of age who used the paste without supervision. The 740 subjects completed the 3-year experiment with an overall 19-percent reduction in the DMFS new caries index. This difference was statistically significant.

Torell and Ericsson (Ref. 16) studied the effect of a sodium monofluorophosphate dentifrice which employed calcium carbonate as the abrasive. The trial utilized 750 Swedish school children, in two groups, one composed of 10-year-old children and the other made up of 11-year-old children. This study, run over a 2-year period, showed that use of the fluoride toothpaste was followed by a reduction in caries which was statistically significant in the older group.

Thus, NaMFP has exhibited an ability to reduce significantly the incidence of new carious lesions with a variety of abrasives; insoluble sodium metaphosphate, dicalcium phosphate, alumina, calcium carbonate, silica, and calcium pyrophosphate. This also involved some variation in pH since this is largely determined by the abrasive system. Although pH may be a factor in the reaction between NaMFP and hydroxyapatite, these clinical trials do not suggest a significant difference in anticaries benefit (Ref. 17).

(3) *Dosage.* Adults and children 2 years of age and older, brush teeth thoroughly at least once daily with 0.76 percent sodium monofluorophosphate in a suitable dentifrice formulation.

(4) *Labeling.* The Panel recommends the Category I labeling. (See part III. paragraph B.1. below—Category I Labeling.)

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c. *Stannous fluoride (dentifrice).* The Panel concludes that 0.4 percent stannous fluoride with a compatible abrasive in a dentifrice product is safe and effective for OTC use as an anticaries agent when marketed in packages containing not more than 260 mg of fluorine.

(1) *Safety.* The toxicity of fluoride and the ingestion of fluoride during toothbrushing has been discussed previously. (See part III. paragraph B.1.a.(1) above—Safety.)

Because stannous fluoride may differ in toxicity from sodium fluoride and sodium monofluorophosphate because of the tin ion, some comments on the acute and chronic toxicity of stannous fluoride may be pertinent. The LD_{50} for mice ingesting stannous fluoride in aqueous solution was found to vary from 169 mg/kg (Ref. 1). to 246 mg/kg (Ref. 2). For rats the LD_{50} was 260 mg/kg (Ref. 1). Levels of stannous fluoride providing up to 18 ppm fluoride in the drinking water or 8 ppm fluoride in the diet for a 140-day period did not inhibit growth or incisor pigmentation in rats. Levels above 9 ppm fluoride in food adversely affected growth and incisor pigmentation and at levels of 150 ppm fluoride some animals died (Ref. 3). Tin from tin salts was reported to have a no-effect level in rats at 22–33 mg/kg and guinea pigs survived on a diet containing 777 ppm tin as tin salt (Ref. 3).

The presence of the stannous ion in stannous fluoride dentifrice formulations may cause some staining of plaque and debris accumulation on the teeth. This has been reported in a number of clinical studies in which an attempt was made to determine the level of staining (Refs. 4, 5, and 6). However, the frequency and intensity of staining with the level of tin present in these formulations does not appear to present any significant problem; therefore, no warning on staining is required for stannous fluoride dentrifice formulations (Ref. 7).

(2) *Effectiveness.* Stannous fluoride at a level of 0.4 percent has been incorporated into dentifrice formulations with a number of abrasive agents including calcium pyrophosphate, insoluble sodium metaphosphate, and silica. These formulations have been subjected to clinical testing and the data from these studies generally indicate that these products are effective in the prevention of dental decay.

The majority of the clinical tests have been conducted with the stannous fluoride dentifrice formulations containing a compatible calcium pyrophosphate abrasive. The studies are too numerous to describe individually or to cite completely. Horowitz and Heifetz (Ref. 8) in their review on dentifrices, listed 12 clinical studies with this abrasive system. This is not a complete listing of all of the studies published in the dental literature because several of the short-term (less than 2-year duration) studies are not included. Although the data from the large majority of the reported studies have demonstrated a statistically significant difference in caries reduction between the test and control groups, a few indicate no significant decrease in caries increments (Refs. 9 and 10).

Dentifrice formulations containing 0.4 percent stannous fluoride with insoluble sodium metaphosphate as the abrasive have also been rather extensively studied in clinical trials (Refs. 4 and 11 through 14). These studies generally indicate a statistically significant reduction in the incidence of dental decay.

The stannous fluoride (0.4 percent) formulations with the silica abrasive system have also been subjected to two human studies. These studies demonstrated the availability of fluoride ion in a fluoride dentifrice with a silica abrasive system (Ref. 15).

(3) *Dosage.* Adults and children 2 years of age and older, brush teeth thoroughly at least once daily with 0.4 percent stannous fluoride in a suitable dentifrice formulation.

(4) *Labeling.* The Panel recommends the Category I labeling. (See part III. paragraph B.1. below—Category I Labeling.)

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d. *Acidulated phosphate fluoride (rinse).* The Panel concludes that an aqueous solution of acidulated phosphate fluoride, derived from sodium fluoride acidulated with a mixture of sodium phosphate, monobasic (NaH_2PO_4) and phosphoric acid to a level of 0.1 molar phosphate ion and a pH of 3.0 to 4.5 which yields an effective fluoride ion concentration of 0.02 percent is a safe and effective dental rinse for OTC use as an anticaries agent when marketed in packages containing not more than 120 mg of fluorine.

(1) *Safety.* The toxicity of fluoride has been discussed previously. (See part III. paragraph B.1.a.(1) above—Safety.)

The total amount of fluorine in a marketed dental rinse can be restricted to a safe quantity for OTC use. In 1958, the Council on Dental Therapeutics of the American Dental Association first recommended that no more than 120 mg of fluorine should be dispensed at any one time (Ref. 1). Such an amount represents a reasonable safety factor to be applied to a dental rinse which is packaged in a single container (Ref. 1). Experience during the past 20 years has borne out the safety of the Council's precautionary limit of fluorine.

Developing teeth of children under 6 years of age may show objectionable dental fluorosis from repeated ingestion of excessive amounts of fluoride. Epidemiological and clinical findings, however, indicate that the formative state of teeth of children 6 years of age and older (excepting third molars) is too advanced to be affected by excessive daily fluoride ingestion (Refs. 2, 3, and 4). Thus, the daily use of a fluoride rinse by children age 6 and above poses little, if any, risk of producing dental fluorosis. Also, it has been shown that children 6 years of age have developed control of their swallowing reflex and are able to rinse for 1 minute and expectorate properly (Ref. 5). Therefore, these products are recommended for OTC use only by persons 6 years and older.

Considerations of the acute and chronic toxic effects of excessive ingestion of a 0.05-percent neutral sodium fluoride aqueous solution (0.023 percent fluoride ion) are applicable to an acidulated-phosphate sodium fluoride aqueous solution containing 0.02 percent fluoride ion. None of the investigators reporting on studies of acidulated phosphate fluoride rinses has attributed harmful local or systemic effects to the use of such rinses. The clinical studies, as listed in the effectiveness section below, have been conducted for periods up to 3 years and have involved daily use of rinses containing approximately 0.02 percent fluoride ion.

In a study in which an acidulated phosphate fluoride gel with a pH of 4.5 and containing 1.1 percent sodium fluoride was applied to 500 children's teeth in custom fitted applicators for 6 minutes each school day for 2 academic years, no harmful local or systemic effects could be attributed to the gel (Ref. 6). In this same study, collodion

replicas of incisor tooth surfaces were made at various periods during the study and no etching of tooth enamel could be detected. Also, tests did not show an increase in urinary fluoride excretion.

(2) *Effectiveness.* A number of clinical studies have demonstrated that repeated mouth rinsing with aqueous acidulated phosphate fluoride solutions can provide an anticariogenic effect in children (Refs. 7 through 13). The fluoride ion concentration of the rinses for daily use studied most frequently was 0.02 percent and for weekly use was 0.1 percent. One study was conducted in a fluoridated community (Ref. 13). The remainder were in nonfluoridated areas. Caries reduction benefit varied from 23 percent in a fluoridated community (Ref. 13) to 30 percent in a nonfluoridated area (Ref. 8).

The FDA Dental Drug Products Advisory Committee has also recognized aqueous solutions of acidulated phosphate fluoride with a pH of approximately 4, that yield a fluoride ion concentration of approximately 0.02 percent, as effective when applied once daily to the teeth as a rinse (39 FR 17245), as has the Council on Dental Therapeutics of the ADA (Ref. 14).

(3) *Dosage.* Adults and children 6 years of age and older, once a day rinse with 10 mL of a 0.02 percent fluoride ion solution between the teeth for 1 minute and then spit out.

(4) *Labeling.* The Panel recommends the Category I labeling. (See part III. paragraph B.1. below—Category I Labeling.)

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e. *Sodium fluoride (rinse).* The Panel concludes that an aqueous solution of 0.05 percent sodium fluoride, having a pH of approximately 7, is a safe and effective dental rinse for OTC use as an anticaries agent when marketed in packages containing a maximum of 120 mg of fluorine.

(1) *Safety.* The toxicity of fluoride and safety considerations of the rinse dosage form have been discussed previously. (See part III. paragraphs B.1.a. (1) and B.1.d. (1) above—Safety.)

A clinical study reported in 1967 indicated that children rinsing fortnightly with a 0.5-percent solution of sodium fluoride over a 3-year period had increased gingivitis levels (Ref. 1). Subsequent clinical studies, however, have not substantiated this finding (Refs. 2, 3, and 4). These studies, some of which were conducted for several years with sodium fluoride concentrations of up to 0. 5 percent, have not revealed adverse effects on gingival tissues or oral mucosa.

(2) *Effectiveness.* A number of clinical studies have demonstrated the anticaries effectiveness of daily rinsing with 0.05-percent sodium fluoride solutions (0.02 percent fluoride ion) for periods up to 3 years (Refs. 3, 5, and 6).

Caries reductions in these studies have ranged from 27 to 50 percent. Other studies utilizing sodium fluoride rinse solutions up to an approximate maximum of 0.3 percent fluoride ion on a weekly or fortnightly basis have also provided evidence of effective caries reduction (Refs. 7 through 13).

The FDA Dental Drug Products Advisory Committee has recognized aqueous solutions of 0.05 percent sodium fluoride with a pH of approximately 7 as safe and effective in reducing the incidence of dental caries when applied daily to the teeth as a rinse (39 FR 17245), as has the ADA's Council on Dental Therapeutics (Ref. 14).

(3) *Dosage.* Adults and children 6 years of age and older, once a day rinse 10 mL of a 0.05-percent sodium fluoride solution between the teeth for 1 minute and then spit out.

(4) *Labeling.* The Panel recommends the Category I labeling. (See part III. paragraph B.1. below—Category I Labeling.)

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f. *Stannous fluoride (rinse).* The Panel concludes that stannous fluoride in a 0.1-percent dental rinse is safe and effective for OTC use as an anticaries agent when marketed in packages containing not more than 120 mg of fluorine. The Panel recognizes that stannous fluoride is unstable as an aqueous solution and that stannous fluoride should therefore be provided in a stable form which when mixed with water as directed immediately before using, results in a 0.1-percent stannous fluoride solution

(1) *Safety.* Toxicity of fluoride and safety considerations of the rinse dosage form have been discussed previously. (See part III. paragraphs B.1.a.(1) and B.1.d.(1) Above—Safety.)

Safety related to the stannous ion was also discussed in sufficient depth under the discussion of stannous fluoride dentifrice. (See part III. paragraph B.1.c.(1) above—Safety).

(2) *Effectivess.* Findings of five clinical studies on daily rinsing with dilute stannous fluoride solution have been published.

The Gier and Jamison study (Ref. 1) was conducted in a fluoridated area and no significant caries reduction was shown by use of a stannous fluoride rinse. The Corcoran study (Ref. 2), conducted in an area where the water was nonfluoridated, showed significant benefit of the rinse. A study by Hall (Ref. 3) evaluated only the effect on plaque formation. Swerdloff and Shannon (Ref. 4) conducted a 5-month study which purported to measure incremental decay. Only one of the published reports to date can be used to strongly support the effectiveness of daily rinsing with a 0.1-percent stannous fluoride solution. In that study, Radike et al. (Ref. 5) found that the rinse reduced decay by aproximately 38 percent (average of two independent examiners) when used daily in school for 20 months by children in a fluoridated community. Aditionally, data from an unpublished 26-month study submitted to the Panel evaluated the cariostatic effectiveness from daily rinsing with 0.04 and 0.08 percent stannous fluoride in a nonfluoridated area. In this study, McCombie et al. (Ref. 6), showed significantly lower caries incidence (by all parameters tested) in children using a rinse with a concentration of 0.04 percent stannous fluoride but less consistent results occurred with the rinse containing 0.08 percent stannous fluoride.

Thus with the four studies conducted for an adequate time interval, two studies showed positive results, results of one study were generally but not consistently positive, and in another study the stannous fluoride rinses did not reduce caries incidence. The results of studies of effectiveness of dental rinses of stannous fluoride 0.04 to 0.1 percent have been inconsistent but tend to suggest efectiveness in preventing carious lesions, especially in children living in nonfluoridated areas. Only one large study of adequate duration has been published in other than abstract form.

Stannous fluoride (SnF_2) is freely soluble in water. Aqueous solutions of the drug are unstable (Refs. 7 and 8), forming a white precipitate within a few hours after preparation (Ref. 8). They should therefore be used promptly after they are prepared (Ref. 8). Older solutions of stannous fluoride have been reported to be as effective or more effective in reducing enamel solubility than fresh solutions, possibly because of increased acidity resulting from hydrolysis following oxidation (Refs. 9 and 10). However, relative decrease in enamel solubility may or may not affect clinical effectiveness, and until further data establish clinical effectiveness of aged aqueous solutions, aqueous stannous fluoride solutions should be freshly prepared. Solutions of stannous fluoride in anhydrous glycerin were stable over a 15-month test period, whereas aqueous solutions lost two-thirds to three-fourths of their stannous tin content during this same period (Ref. 10).

Unlike sodium fluoride or acidulated phosphate fluoride, stannous fluoride produces extrinsic staining of the teeth in some individuals. In the 2-year study of daily rinsing in a fluoridated community, staining was observed (Ref. 5). Yellow staining of teeth in mouths with poor oral hygiene occurred more noticeably in the test group than in the control group. Because of the risk of staining, stannous fluoride rinse is required to have a statement on the label regarding stain.

(3) *Dosage.* Adults and children 6 years of age and older, once a day rinse 10 mL of a freshly prepared aqueous solution of 0.1 percent stannous fluoride between the teeth for 1 minute and then spit out.

(4) *Labeling.* The Panel recommends Category I labeling. (See part III. paragraph B.1. below—Category I Labeling.) In addition, the Panel recomends the following statements for stannous fluoride mouth rinse products:

(i) "This product may produce surface staining of the teeth. Adequate toothbrushing may prevent these stains which are not harmful or permanent and may be removed by your dentist."

(ii) "Use immediately after preparing the rinse."

(iii) For powder or effervescent tablets: "Do not use as a rinse until all the material has dissolved."

The labeling must also include directions, for the preparation of these dental rinse solutions before use, which are clear, direct, and provide the consumer with sufficient information to permit the safe and effective use of the product.

References

(1) Gier, R. E., and H. C. Jamison, "The Effect of a Stannous Fluoride Mouthwash on Caries Increments," *Journal of Dental Research*, 52:232, 1973.

(2) Corcoran, J. W., "Comparison of Cariostatic Effectiveness of Two Concentrations of SnF_2 Mouthwash," *Journal of Dental Research*, 53:163, 1974.

(3) Hall, G. L., "Stannous Fluoride (0.1%) Mouthwash Study," USAF School of Aerospace Medicine, San Antonio, TX, 1968.

(4) Swerdloff, G., and I. L. Shannon, "Feasibility of the Use of Stannous Fluoride Mouthwash in a School System," *Journal of Dentistry for Children*, 36:363–368, 1969.

(5) Radike, A. W., et al., "Clinical Evaluation of Stannous Fluoride as an Anticaries Mouthrinse," *Journal of the American Dental Association*, 86:404–408, 1973.

(6) OTC Volume 080149.

(7) Council on Dental Therapeutics, "Accepted Dental Therapeutics", 37th Ed., American Dental Association, Chicago, pp. 300–301, 1975.

(8) Shannon, I. L., "Water-Free Solutions of Stannous Fluoride and their Incorporation into a Gel for Topical Application," *Caries Research*, 3:339–347, 1969.

(9) Shannon, I. L., "Effect of Storage on the Laboratory Performance of Aqueous Solutions of Stannous Fluoride," *Journal of Southern California State Dental Association*, 32:67–69, 1964.

(10) Horowitz, H. S., and S. B. Heifetz, "The Current Status of Topical Fluorides in Preventive Dentistry," *in* "Fluorides and Dental Caries," Edited by Newbrun, E., Charles C. Thomas, Springfield, IL, pp. 34–59, 1972.

g. *Stannous fluoride (gel).* The Panel concludes that stannous fluoride nondentrifrice dental gels containing 0.4 percent stannous fluoride in an anhydrous glycerin gel are safe and effective for OTC use as anticaries agents when marketed in packages containing not more than 120 mg of fluorine.

(1) *Safety.* Toxicity of fluoride has been discussed previously. (See part III. paragraph B.1.a. (1) above—Safety.) The safety of stannous fluoride has also been discussed previously. (See part III. paragraph B.1.c. above—Stannous fluoride (dentifrice).)

(2) *Effectiveness.* Four studies on stannous fluoride dental gels containing 0.4 percent stannous fluoride in anhydrous glycerin have been published (Refs. 1 through 4). Two of these studies (Refs. 1 and 2) measured reduction of enamel solubility of teeth treated for various periods prior to extraction. The Landry and Shannon study (Ref. 1) compared the enamel solubility of teeth of 28 children who brushed once daily for 1 to 7 weeks with stannous fluoride gel and the enamel solubility of control teeth extracted prior to the fluoride treatment. Statistically significant reduction in enamel solubility occurred with the "longer" treatment periods.

The Feller study (Ref. 2) compared enamel solubility of teeth of adults using stannous fluoride gels for 1 to 5 weeks with teeth extracted from the same adults prior to treatment with the gel. Application of the gel resulted in enamel solubility reduction.

In Miller and Shannon's study (Ref. 3) a small number of patients who had received irradiation for malignancies of the head and neck applied a 0.4-percent stannous fluoride gel to their teeth once daily with a plastic carrier or a toothbrush. The eight patients treated for 12 months developed no carious lesions whereas the two patients who refused treatment developed caries.

Stratemann and Shannon (Ref. 4) compared the incidence of decalcification in teeth of children treated with 0.4-percent stannous fluoride gel with untreated controls. The 99 treated children and the 110 control children all wore orthodontic bands. Results showed that incidence of decalcification was 58 percent in the control group and 2 percent in the 59 patients why used the gel daily as directed. Of the 19 children who used the gel only two or three times per week, 26 percent had decalcified areas.

Stannous fluoride is stable in anhydrous glycerin (Ref. 5). Gels may be formulated by the addition of a compatible thickening agent to the glycerin vehicle. Stannous fluoride gels must also conform to viscosity stability requirements according to good manufacturing practices.

The studies cited above provide reasonable documentation of effectiveness of the dental gel dosage form.

(3) *Dosage.* Adults and children 6 years of age and older, once a day apply 0.4 percent stannous fluoride in a nondentifrice anhydrous glycerin gel to your teeth.

(4) *Labeling.* The Panel recommends the Category I labeling. (See part III. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following statements for stannous fluoride dental gel products: (i) "This product is not a dentifrice."

(ii) "This product may produce surface staining of the teeth. Adequate toothbrushing may prevent these stains which are not permanent or harmful and may be removed by your dentist."

References

(1) Landry, D. F., and I. L. Shannon, "A Home-care Program of Chemical Preventive Dentistry for Orthodontic Patients," *American Journal of Orthodontics,* 63:12–17, 1973.

(2) Feller, R. P., "Reduction of Enamel Solubility by Daily Use of a 0.4% Stannous Fluoride Gel," *Journal of Dental Research,* 53:1280–1283, 1974.

(3) Miller, J. T., and I. L. Shannon, "A Clinical Report: Water-free Stannous-fluoride Gel and Post-irradiation Caries," *Public Health Dentistry,* 32:127, 1972.

(4) Stratemann, M. W., and I. L. Shannon, "Control of Decalcification in Orthodontic Patients by Daily Self-administered Application of a Water-free 0.4 percent Stannous Fluoride Gel," *American Journal of Orthodontics,* 66:273–279, 1974.

(5) Shanon, I. L., "Water-Free Solutions of Stannous Fluoride and their Incorporation into a Gel for Topical Application," *Caries Research,* 3:339–347, 1969.

Category I Labeling

The Panel recommends the following Category I labeling for anticaries active ingredients:

a. *Dentifrices.*

(1) *Indications.* "Aids in the prevention of dental caries (decay or cavities)."

(2) *Directions.* "Adults and children 2 years of age and older, brush teeth thoroughly at least once daily or as directed by a dentist or physician. Children under 6 years of age should be supervised in the use of this product."

(3) *Package limit.* Dentifrice packages should not contain more than 260 mg total fluorine.

(4) *Other allowable statements.* The labeling may also include, where the product has been approved by ADA, the statement: "(Product name) has been shown to be an effective decay-preventive dentifrice that can be of significant value when used in a conscientiously applied program of oral hygiene and regular professional care."

b. *Dental rinses.*

(1) *Indications.* "Aids in the prevention of dental caries (decay or cavities)."

(2) *Warning.* "Do not swallow. Developing teeth of children under 6 years of age may become permanently discolored if excessive amounts of fluoride are repeatedly swallowed."

(3) *Directions.* "Use as follows or as directed by a dentist or physician: Adults and children 6 years of age and older, once a day rinse 10 mL between the teeth for 1 minute and then spit out. Do not eat or drink for 30 minutes."

(4) *Additional labeling statements for dental rinses*—(i) *For all dental rinses.* "This product is not a dentifrice."

(ii) *For stannous fluoride products intended for use as a rinse—(a) For all stannous fluoride products intended for use as a rinse. (1)* "This product may produce surface staining of the teeth. Adequate toothbrushing may prevent these stains which are not harmful or permanent and may be removed by your dentist."

(2) "Use immediately after preparing the rinse."

(b) For powder or effervescent tablets used to prepare rinses. "Do not use as a rinse until all the material has dissolved."

(5) *Package limit.* Dental rinse packages should not contain more than 120 mg total fluorine.

c. *Dental gels.*

(1) *Indications.* "Aids in the prevention of dental caries (decay or cavities)."

(2) *Warning.* "Do not swallow. Developing teeth of children under 6 years of age may become permanently discolored if excessive amounts of fluoride are repeatedly swallowed."

(3) *Directions.* "Use as follows or as directed by a dentist or physician: Adults and children 6 years of age and older, once a day following cleansing of your teeth, apply the gel to your teeth. Brush thoroughly and allow gel to remain on the teeth for 1 minute and then spit out. Do not eat or drink for 30 minutes."

(4) *Additional labeling statements for dental gels*—(i) *For all dental gels.* "This product is not a dentifrice."

(ii) *For stannous fluoride gels.* "This product may produce surface staining of the teeth. Adequate toothbrushing may prevent these stains which are not harmful and may be removed by your dentist."

(5) *Package limit.* Dental gel packages should not contain more than 120 mg total fluorine.

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

Category II Active Ingredients

Phosphate preparations
Calcium sucrose phosphate (CaSP)
Dicalcium phosphate dihydrate (DCPD)
Disodium hydrogen phosphate
Phosphoric acid
Sodium dihydrogen phosphate
Sodium dihydrogen phosphate monohydrate
Sodium phosphate
Sodium phosphate, dibasic anhydrous reagent
Sodium bicarbonate
Sodium monofluorophosphate (6 percent liquid concentration)

a. *Phosphate preparations.* The Panel concludes that, although the phosphate preparations listed above are safe when used as buffers, fillers, and abrasives, they are not generally recognized as effective for OTC use as anticaries agents. The Panel recommends that phosphate preparations should not be labeled as anticaries agents.

(1) *Safety.* Studies in rats show that the linear condensed phosphates, sodium pyrophosphate, tetrapyrophosphate, and hexametaphosphate, are more toxic than orthophosphates. The toxicity of the linear condensed phosphates is related to hydrolysis and release of phosphoric acid with resultant metabolic acidosis. The cyclic phosphates are not readily hydrolyzed in body fluids and do not release sufficient phosphoric acid to produce metabolic acidosis. Among the organic phosphates, the cyclic phosphates rank with the orthophosphates as the least toxic; they are well tolerated in large doses (Ref. 1).

Studies of acute toxic effects of phosphates in other species are relatively sparse. A Franklin Institute report (Ref. 2) summarizes a study in dogs treated daily for 1-month periods with the sodium salts, of hexameta-, tripoly-, trimeta-, and tetrametaphosphate. At doses of only 4 mg/kg, a variety of toxic effects were seen including renal tubule injury.

A few reports are available regarding toxicity in humans. One report described a 6-week-old infant who became comatose after accidental ingestion of a proprietary laxative containing sodium phosphate/sodium biphosphate (Ref. 3). Another report involved an inorganic phosphate laxative poisoning resulting in tetany in a 3-month-old infant (Ref. 4). Cases of phosphate toxicity have also been reported to occur in adults (Refs. 5 through 8).

The average adult consumes in excess of 1.5 g phosphorus daily and 2 to 3 g daily might represent the usual intake. An extreme diet containing maximum quantities of additives and naturally occuring phosphorus could supply from 6 to 7 g daily. The saline cathartic effects of large doses of these materials tend to limit absorption and the potential for absorption of toxic levels.

In general, unless homeostatic mechanisms are overloaded, these materials are regarded as safe (Ref. 2).

(2) *Effectiveness.* The evidence is nearly unanimous that phosphates are effective anticaries agents in animals. Their cariostatic activity differs depending upon the types of anion (cyclic-, trimeta-, tripoly-, hexameta-, ortho-, and pyrophosphate), the activity decreasing approximately in the order given. Phosphates of the same series differ in cariostatic activity depending upon the type of cation (H, Na, K, Ca, Mg), the activity decreasing in the order given. Their cariostatic effect appears to be largely due to a local action on the tooth as the agents pass through the mouth, or a systemic-local action when they are returned to the mouth in the saliva. It is thought that the phosphates alter the structure of enamel, possibly by an initial demineralizing and subsequent remineralizing process producing changes in enamel morphology (Ref. 9).

The effect of phosphates on human teeth seems to be more complex and inconclusive than the effects in experimental animals. Whereas fluorides, for example, have been shown to persist for long periods of time following a single exposure, the phosphate data are not as clear-cut (Ref. 10). Larson et al. (Ref. 11) suggest that, among the phosphate anions, trimetaphosphate may achieve long retention and that continuous exposure may not be a requirement for cariostatic activity. Unlike the fluoride ion, phosphates have not been shown to enter into tooth structure and alter its physical characteristics. Frequent exposure may therefore be the key to anticaries activity of phosphate in humans.

(3) *Evaluation.* Because phosphates have never previously been marketed as anticaries dental products and because there is no evidence that phosphates are effective anticaries agents in humans, the Panel recommends placing phosphates in Category II.

References

(1) Gosselin, R. E., et al., "Metabolic Acidosis and Hypocalcemia as Toxic Manifestations of Polymeric Phosphates," *Journal of Pharmacology and Experimental Therapeutics,* 108:117–127, 1953.

(2) Walter, P. C., J. E. Villaume, and T. J. Taylor, "Phosphates: A Monograph," National Technical Information Service, Springfield, VA, PB–221, No. 224/9, p. 47, 1975.

(3) Smith, M. S., K. W. Feldman, and C. T. Furukawa, "Coma in an Infant due to Hypertonic Sodium Phosphate Medication," *The Journal of Pediatrics,* 82:481–482, 1973.

(4) Levitt, M., C. Gessert, and L. Finberg, "Inorganic Phosphate (Laxative) Poisoning Resulting in Tetany in an Infant," *The Journal of Pediatrics,* 82:479–481, 1973.

(5) Goldfinger, P., "Hypokalemia, Metabolic Acidosis, and Hypocalcemic Tetany in a Patient Taking Laxatives: A Case Report," *Journal of the Mount Sinai Hospital,* 36:113–116, 1969.

(6) McConnell, T. H., "Fatal Hypocalcemia from Phosphate Absorption from Laxative Preparation," *Journal of the American Medical Association,* 216:147–148, 1971.

(7) Breuer, R. I., and J. LeBauer, "Caution in the Use of Phosphates in the Treatment of Severe Hypercalcemia," *Journal of Clinical Endocrinology,* 27:697–698, 1967.

(8) Shackney, S., and J. Hasson, "Precipitous Fall in Serum Calcium, Hypotension, and Acute Renal Failure after Intravenous Phosphate Therapy for Hypercalcemia: Report of Two Cases," *Annals of Internal Medicine,* 66:906–916, 1967.

(9) Nizel, A. E., and R. S. Harris, "The Effects of Phosphates on Experimental Dental Caries: A Literature Review," *Journal of Dental Research,* 43:1123–1136, 1964.

(10) DePaola, P. F., "A Review of Clinical Trials Utilizing Acidulated Phosphate-Fluoride Topical Agents," *Journal of the American College of Dentists,* 35:22–33, 1968.

(11) Larson, R. H., et al., "Continuous Versus Intermittent Feedings of Different Levels of Trimetaphosphate in Relation to Caries Development in the Rat," *Archives of Oral Biology, 17:1537–1541, 1972.*

b. *Sodium bicarbonate.* The Panel concludes that sodium bicarbonate is safe when used in a dentifrice but there is no evidence to document the effectiveness of the compound relative to reduction of dental caries and the remineralization of tooth structure. Sodium bicarbonate is odorless and consists of small, opaque, monoclinic crystals of white powder; when dissolved it has an alkaline reaction and

saline taste. Each gram represents 11.9 millequivalent sodium. When heated to 250° to 300° F it decomposes and is converted to anhydrous sodium carbonate (Ref. 1). The Panel recommends that sodium bicarbonate should not be labeled as an anticaries agent.

(1) *Safety.* The irritation and hypersensitivity potential is essentially zero as is teratogenicity and carcinogenicity. The amounts ordinarily used in tooth brushing, even if swallowed, would not produce any adverse effects.

(2) *Effectiveness.* Sodium bicarbonate is widely used as a gastric antacid, as a urinary or systemic alkalizer, as an aqueous wash locally, and as a topical antipruritic solution or paste (Ref. 2).

Although it is known to have mild abrasive properties and has been used as a dentifrice for many years (Ref. 2), the Panel finds on evidence that the antacid effects of sodium bicarbonate on the teeth are more than transitory nor that it has any anticaries effect.

(3) *Evaluation.* The Panel concludes that sodium bicarbonate as a dentifrice is safe but has no known anticaries effect. The Panel recommends placing sodium bicarbonate in Category II.

References

(1) Stecher, P. G., "Merck Index," 8th Ed., Merck and Co., Rahway, NJ, p. 142, 1968.

(2) Council on Dental Therapeutics, "Accepted Dental Therapeutics," 37th Ed., American Dental Association, Chicago, p. 240, 1977.

c. *Sodium monofluorophosphate (6 percent liquid concentration).* The Panel concludes that use of 0.24 mL of a 6-percent concentration of sodium monofluorophosphate in a liquid product to be applied with a toothbrush would appear to provide an opportunity for the regular ingestion of about 2 mg of fluorine per day.

(1) *Safety.* In order to prevent excessive OTC use of fluoride products which may cause adverse effects (fluorosis), the Panel recommends that this product be used on prescription only.

(2) *Effectiveness.* This liquid dosage form and concentration (6 percent) of sodium monofluorophosphate may be effective.

(3) *Evaluation.* The Panel concludes that although this preparation may be effective, it cannot be generally recognized as safe for use in the OTC drug market. The Panel recommends placing sodium monofluorophoshate (6 percent liquid concentration) in Category II.

Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety or effectiveness of the product are unsupported by scientific data and in some instances by sound theoretical reasoning.

The Panel considers the following examples of claims to be misleading and unsupported by scientific data:

(1) "For a healthier mouth with less decay."

(2) "Raising your natural resistance to tooth decay."

(3) "Reduces mouth acidity."

3. *category III conditions for which the available data are insufficient to permit final classification at this time.*

None.

FDA has determined that his 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 Part 355, to read as follows:

PART 355—ANTICARIES DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Sec.

Subpart B—Active Ingredients

Subpart C—[Reserved]

Supart 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

§ 355.1 Scope.

An over-the-counter anticaries drug product in a form suitable for topical administration to the teeth is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this Part 355 in addition to each of the general conditions established in § 330.1 of this chapter.

§ 355.3 Definitions.

(a) *Abrasive.* Solid materials which are added to dentifrices to facilitate mechanical removal of dental plaque, debris, and stain from tooth surfaces.

(b) *Anticaries agent.* An agent which aids in the prevention of dental caries (decay or cavities).

(c) *Dental caries.* A disease of calcified tissues of teeth characterized by demineralization of the inorganic portion and destruction of the organic matrix.

(d) *dental gel.* A dosage form for delivering an anticaries agent to the teeth. Dental gels are formulated in an anhydrous glycrin base with suitable thickening agents included to adjust viscosity. Dental gels do not contain abrasives and are not intended for use in cleaning the teeth.

(e) *Dental rinse.* A liquid dosage form for delivering and anticaries agent to the teeth.

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

(g) *Fluoride.* The inorganic form of the chemical element fluorine in combination with other elements.

(h) *Fluoride ion.* The negatively charged atom of the chemical element fluorine.

Subpart B—Active Ingredients

§ 355.10 Anticaries active ingredients.

The following ingredients are generally recognized as safe and effective for use in OTC anticaries drug products when marketed within the doage limits forms established for each ingredient:

(a) *dentfrices.*

(1) Sodium fluoride 0.22 percent.

(2) Sodium monofluorophosphate 0.76 percent.

(3) Stannous fluoride 0.4 percent.

(b) *Dental rinses.*

(1) Acidulated phosphate fluoride derived from sodium fluoride acidulated with a mixture of sodium phosphate, monobasic, and phosphoric acid to a level of 0.1 molar phosphate ion and a pH of 3.0 to 4.5 and which yields an effective fluoride ion concentration of 0.02 percent.

(2) Sodium fluoride 0 05-percent aqueous solution.

(3) Stannous fluoride marketed in a stable form and containing adequate directions for mixing with water immediately before using to result in a 0.1-percent solution.

(c) *Dental gel.* Stannous fluoride 0.4 percent in an anhydrous glycerin gel, made from anhydrous glycerin and the addition of suitable thickening agents to adjust viscosity.

§ 355.20 Package size limitations.

Due to the toxicity associated with fluoride active ingredients, the following package size limitations are required for anticaries products: (a) *Dentifrices.* Dentifrice packages should not contain more than 260 milligrams total fluorine.

(b) *Dental rinses and dental gels.* Dental rinse and gel packages should not contain more than 120 milligrams total fluorine.

Subpart C—[Reserved]

Subpart D—Labeling

§ 355.50 Labeling of anticaries drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "Anticavity (*insert dentifrice, dental rinse, or dental gel as applicable*)."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the phrase "Aids in the prevention of dental caries (decay or cavities)."

(c) *Warnings.* The labeling of the dental rinse or dental gel products contains the following warning under the heading "Warnings": "Do not swallow. Developing teeth of children under 6 years of age may become permanently discolored if excessive amounts of fluoride are repeatedly swallowed."

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

(1) *For anticaries products marketed in a dentifrice dosage form.* "Adults and children 2 years of age and older, brush teeth thoroughly at least once daily or as directed by a dentist or physician. Children under 6 years of age should be supervised in the use of this product"

(2) *For anticaries products marketed for use as dental rinses.* "Adults and children 6 years of age and older, once a day rinse 10 milliliters between the teeth for 1 minute and then spit out. Do not eat or drink for 30 minutes."

(3) *For stannous fluoride products intended for use as dental rinses.* (i) "Use immediately after preparing the rinse."

(ii) *For powder or effervescent tablets used to prepare rinses.* "Do not use as a rinse until all the material has dissolved."

(4) *For anticaries products marketed as dental gels.* "Adults and children 6 years of age or older, once a day following cleansing of your teeth, apply the gel to your teeth. Brush thoroughly and allow gel to remain on the teeth for 1 minute and then spit out. Do not eat or drink for 30 minutes."

(e) *Additional labeling statements for anticaries products.* The following labeling statements need not appear under warnings but are required to apper on the label of anticaries products as applicable.

(1) *For all dental rinses and gels.* "This product is not a dentifrice."

(2) *For all stannous fluoride products intended for use as dental rinses or dental gels.* "This product may produce surface staining of the teeth. Adequate toothbrushing may prevent these stains which are not harmful or permanent and may be removed by your dentist."

(f) *Other allowable statements for anticaries dentifrice products.* The labeling may also include, where the product has been approved by the American Dental Association (ADA), the statement: "(Product name) has been shown to be an effective decay-preventive dentifrice that can be of significant value when used in a conscientiously applied program of oral hygiene and regular professional care."

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 June 26, 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 July 28, 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: March 17, 1980.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

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