DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 355

[DOCKET NO. 80N-0042]

Anticaries Drug Products for Over-the-Counter Human Use; Tentative Final Monograph

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) anticaries drug products (drug products that aid in the prevention of dental cavities) are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by November 29, 1985. New data by September 30, 1986. Comments on the new data by December 1, 1986. These dates are consistent with the time periods specified in the agency's revised procedural regulations for reviewing and classifying OTC drugs (21 CFR 330.10). Comments on the agency's economic impact determination by January 28, 1986.

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

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drugs and Biologics (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of March 28, 1980 (45 FR 20666) FDA published, under §330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC anticaries drug products, together with the recommendations of the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by June 26, 1980. Reply comments in response to comments filed in the initial comment period could be submitted by July 28, 1980.

In accordance with §330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information. In response to the advance notice of proposed rulemaking, the Panel Chairman, four drug manufacturers' associations, ten drug manufacturers, one consumer, seven health care professionals, two health care professional societies, and one coalition opposed to fluoridation submitted comments. Copies of the comments received are on public display in the Dockets Management Branch.

FDA is issuing the tentative final monograph for OTC anticaries drug products in two segments. This document is the first segment to be published, and it contains the agency's responses to general comments on anticaries drug products, comments on the switch of prescription anticaries drug products to OTC status, comments on specific anticaries active ingredients, comments on dosages for anticaries active ingredients, and comments on the labeling of anticaries drug products.

The second segment of the tentative final monograph on OTC anticaries drug products will be published in a future issue of the **Federal Register** and will contain the agency's proposals regarding final formulation testing, i.e., "Laboratory Testing Profiles," for Category I active ingredients in dentifrice formulations, and issues relating to this testing. The agency stated in the advance notice of proposed rulemaking that these laboratory testing profiles 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 (45 FR 20666). The agency held an open public meeting on September 26 and 27, 1983 regarding unresolved technical issues concerning the laboratory testing profiles and reopened the administrative record to include the proceedings of the public meeting and to allow comment on matters raised at the meeting (48 FR 38853). The agency will base its decisions concerning these testing profiles on the results of the meeting and other relevant information.

The advance notice of proposed rulemaking, which was published in the **Federal Register** on March 28, 1980 (45 FR 20666), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the present document is designated in the OTC drug review regulations as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule) to establish Part 355 (21 CFR Part 355), FDA states for the first time its position on the establishment of a monograph for OTC anticaries drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC anticaries drug products.

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

The OTC procedural regulations (21 CFR 330.10) have been revised to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). (See the **Federal Register** of September 29, 1981; 46 FR 47730.) The Court in *Cutler* held that the OTC drug regulations were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision has been deleted from the regulations, which now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph.

Although it was not required to do so under *Cutler*, FDA will no longer use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category

III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but will use instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

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

In the advance notice of proposed rulemaking for OTC anticaries drug products (published in the **Federal Register** of March 28, 1980 (45 FR 20666)), the agency suggested that the conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the **Federal Register** and that the conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of whether further testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

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

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

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notice published in the **Federal Register** of August 9, 1972 (37 FR 16029) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

I. The Agency's Tentative Conclusions on The Comments

A. General Comments on Anticaries Drug Products

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

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

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

During the course of the OTC drug review, the agency has maintained that the terms that may be used in an OTC drug product's labeling are limited to those terms included in a final OTC drug monograph. (This policy has become known as the "exclusivity rule.") The agency's position has been that it is necessary to limit the acceptable labeling language to that developed and approved through the OTC drug review process in order to ensure the proper and safe use of OTC drugs. The agency never contended, however, that any list of terms developed during the course of the review literally exhausts all the possibilities of terms that appropriately can be used in OTC drug labeling. Suggestions for additional terms or for other labeling changes may be submitted as comments to proposed or tentative final monographs within the specified time periods or through petitions to amend monographs under § 330.10(a)(12). For example, the labeling proposed in this tentative final monograph has been expanded and revised in response to comments received. (See comments 26 and 27 below.)

During the course of the review, FDA's position on the "exclusivity rule" has been questioned many times in comments and objections filed in response to particular proceedings and in correspondence with the agency. The agency has also been asked by The Proprietary Association to reconsider its position. In a notice published in the **Federal Register** of July 2, 1982 (47 FR 29002), FDA announced that a hearing would be held to assist the agency in resolving this issue. On September 29, 1982, FDA conducted an open public forum at which interested parties

presented their views. The forum was a legislative type administrative hearing under 21 CFR Part 15 that was held in response to a request for a hearing on the tentative final monographs for nighttime sleep-aids and stimulants (published in the **Federal Register** of June 13, 1978; 43 FR 25544).

After considering the testimony presented at the hearing and the written comments submitted to the record, in the **Federal Register** of April 22, 1985 (50 FR 15810), FDA proposed to change its exclusivity policy for the labeling of OTC drug products. As proposed, manufacturers may select one of the following options:

(1) The label and labeling would contain within a boxed area designated "APPROVED USES" the specific wording on indications for use established under an OTC drug monograph. The boxed areas would be required to be displayed in a prominent and conspicuous location. As under the present policy, the labeling in the boxed area would be required to be stated in the exact language of the monograph. However, with this option a statement that the information in the box was published by the Food and Drug Administration would appear either in the box or reasonably close by. At the manufacturer's option, the designation of the boxed area and the statement that the labeling was established by FDA could be combined.

(2) As a complete alternative to using the boxed area designated "APPROVED USES," the proposal would for the first time allow manufacturers an option to use other truthful and nondeceptive statements relating only to the indications established in an applicable monograph subject to the prohibitions in section 502(a) of the act against misbranding by the use of false or misleading labeling. If this alternative is selected, the manufacturer would not be able to use a boxed area or include a statement that the indications are endorsed by the Food and Drug Administration.

(3) As a third alternative, manufacturers could use both a boxed area with the monograph language and also, elsewhere in the labeling, use other non-monograph language that meets the statutory standards of truthfulness and accuracy.

Regardless, other aspects of OTC drug labeling, such as the statement of identity, warnings, and directions, would continue to be required to comply with the monograph, including following any exact language established in the monograph.

The proposal to change the exclusivity policy provides for 90 days of public comment. After considering all comments submitted, the agency will announce its final decision on this matter, in a future issue of the **Federal Register.**

3. One comment contended that the Panel's recommendation that sodium fluoride dental products be packaged in containers with child-resistant closures is not consistent with the Consumer Product Safety Commission's (CPSC) proposal, published in the **Federal Register** of March 19, 1980 (45 FR 17593), that all sodium fluoride drug preparations containing no more than 264 milligrams (mg) of sodium fluoride (120 mg fluorine) be exempt from child-protection packaging requirements for prescription drugs. The comment also noted that aqueous solutions of sodium fluoride are currently exempt from these requirements (16 CFR 1700.14). The comment stated that, while the CPSC's recommendation applies only to prescription drugs, it should be extended to apply to OTC fluoride dental drug products as well.

The Dental Panel recommended that certain fluoride dental rinses and gels, which had been previously restricted to prescription use, be made available OTC provided that they contain no more than 120 mg total fluorine per package, and that they are packaged in containers with child-resistant closures (45 FR 20673 and 20675). In the preamble to the Panel's report, the agency pointed out that CPSC, and not FDA, regulates child-resistant packaging and stated that it would make the CPSC aware of the Dental Panel's recommendations (45 FR 20666). The Panel's report was adopted before the CPSC published its proposed rule on March 19, 1980, but was not published until March 28, 1980.

FDA and CPSC representatives met on June 17, 1980 to establish a coordinated effort to deal with the Panel's recommendations that OTC anticaries fluoride dental rinses and gels be packaged with child-resistant closures in addition to limiting the amount of fluorine contained in a package to 120 mg (Ref. 1). CPSC explained that to implement the Panel's recommendation would require a reversal of exemptions to the requirement of child-resistant closures granted for aqueous solutions of sodium fluoride (16 CFR 1700.14) and the proposed extension of this exemption to all generic forms of sodium fluoride containing no more than 264 mg sodium fluoride (120 mg fluorine) per package in the **Federal Register** of March 19, 1980 (45 FR 17593). CPSC issued a final rule granting this proposed exemption to sodium fluoride drug preparations, including liquid and tablet forms, on November 26, 1980. Its decision was based on extensive data and information on fluoride toxicity that are fully discussed in the final rule (45 FR 78630). These data and information have been entered into the public administrative record for this rulemaking on OTC anticaries drug products (Ref. 1). The agency concurs with the CPS's findings that child-resistant closures for anticaries drug products containing no more than 120 mg fluorine are not necessary. FDA is proposing to limit the size of OTC packages containing fluoride rinses and gels to 120 mg fluorine per package and, therefore, will not request that CPSC consider proposing that fluoride rinses and gels included in this monograph be packaged with child-resistant closures.

Reference

(1) Memorandum coded M, Docket No. 80N-0042, Dockets Management Branch.

4. Three comments requested that dental rinse and nonabrasive dental gel packages be permitted to contain the same amount of fluorine (260 mg) as dentifrice packages instead of being limited to 120 mg of fluorine per package as stated by the Panel in its recommended monograph. Two of the comments argued that over 25 years of worldwide OTC use has confirmed the safety of dentifrice products containing 260 mg of fluorine. One of the comments maintained that dental rinse and nonabrasive gel packages containing 260 mg of fluorine might be safer than a comparable tube of fluoride dentifrice because the dental rinse and nonabrasive gel packages may also have child-proof safety closures. This comment added that it would take about 32 ounces (oz) of a 0.05-percent sodium fluoride dental rinse to contain 260 mg of fluorine, and that it would be as difficult to ingest 32 oz of a dental rinse from a bottle with a child-proof safety closure as it would be to ingest 9 oz of a fluoride dentifrice from a tube. Two of the comments pointed out that the same concentration (0.4 percent) of stannous fluoride is recommended for both the dentifrice and the nonabrasive gel, yet the gel package could contain a total of only 120 mg of fluorine and would require a child-proof safety closure, while the dentifrice package could contain a total of 260 mg of fluorine and would not require a child-proof safety closure. One of the comments stated that it is the prevailing conclusion of toxicologists that none of these dosage forms is any more hazardous than any other, and that the request to increase the allowable fluorine content in dental

rinses and nonabrasive gels was based on extensive pharmacological data.

The Panel stated that since 1958 the Council on Dental Therapeutics of the American Dental Association (ADA) has recommended for dental rinses and gels that no more than 120 mg of fluorine per package be dispensed at any one time because of its possible misuse. Experience during the past 20 years has borne out the safety of the Council's precautionary limit of fluoride for dental rinses and gels (45 FR 20673).

In addition, a significant distinction exists between dentifrices and nonabrasive dental gels and rinses. A dentifrice formulation contains an abrasive (45 FR 20671), while nonabrasive dental gels and rinses do not. As the Panel pointed out, the amount of fluorine available for pharmacological or toxicological action in a dentifrice is dependent upon the chemical reactivity of the fluoride ion with the abrasive (45 FR 20675–20677). Therefore, even if a 9-oz tube of a dentifrice containing 260 mg of fluorine were ingested, the entire 260 mg of fluorine is not available for absorption; only a part is available. In a 32-oz bottle of dental rinse or a 9-oz tube of a nonabrasive dental gel containing 260 mg of fluorine all of the 260 mg of fluorine is in solution and available for absorption. One study concluded that a dentifrice containing a given dose of a soluble fluoride would be 2.5 times safer than an aqueous solution, such as a dental rinse, containing the same dose of soluble fluoride (Ref. 1).

None of the comments submitted data to support the safety of more than 120 mg fluorine in nonabrasive dental gel and dental rinse products. The agency believes that the safety of dentifrices containing up to 260 mg fluorine can be attributed to the likelihood that the amount of dentifrice that contains a toxic dose of fluorine could not be ingested without vomiting (Ref. 2) and to the decreased amount of fluorine actually available for absorption because of the reactivity of fluorine with the abrasives in dentifrices.

Although the Panel recommended child-proof safety closures for dental rinses and gels, the CPSC states that these dosage forms, as well as tablets containing sodium fluoride, are exempt from regulations requiring child-proof safety closures as long as they contain 264 mg of sodium fluoride, which amounts to 120 mg of fluorine, or less per package. As discussed in comment 3 above, the CPSC's decision was based on the low toxicity potential of this amount of sodium fluoride and on the ADA's recommendation of 264 mg of sodium fluoride (120 mg fluorine) as the maximum amount to be dispensed at one time. The agency agrees with the recommendations of the ADA and the Panel and is proposing to limit the total amount of fluorine in packages of OTC dental rinses and nonabrasive gels to not more than 120 mg of fluorine per package.

References

(1) OTC Volume 080098.

(2) OTC Volumes 080018, 080098, and 080099.

5. Two comments had different views on the last sentence in the Panel's definition of fluoride at 45 FR 20671: "The deposition of fluoride in dental enamel has been shown to increase resistance to enamel solubility and therefore dental decay." Although acknowledging that the sentence is correct, one comment maintained that it was a commentary, not a definition, and should be omitted. The other comment stated that it was encouraging to find the statement included in the definition because it firmly established the clinical relationship between enamel solubility and tooth decay.

The definition discussed by the comments was not included in the Panel's recommended monograph, but was included in its report to reflect the Panel's intended meaning of fluoride in referring to OTC anticaries drug products. The agency acknowledges the definition in the Panel's report, but is adopting in this tentative final monograph the definition of fluoride recommended by the Panel in § 355.3: "The inorganic form of the chemical element fluoride in combination with other elements."

6. One comment suggested changing the first sentence in § 355.10, "The following ingredients are generally recognized as safe and effective for use in OTC anticaries drug products when marketed within the dosage limits forms established for each ingredient," to read as follows: "The following ingredients are generally recognized as safe and effective for use in OTC anticaries drug products when included in a suitable vehicle . . . and marketed within the dosage limits and in the forms established for each ingredient."

The sentence in § 355.10 was unclear as a result of a printing error. The agency proposes to word this sentence as follows in this tentative final monograph: "The active ingredient of the product consists of any of the following, within the established concentration and dosage form." This statement is compatible with the intent of the sentence suggested by the comment and consistent with other tentative final monographs.

7. One comment, while recognizing that the example list of inactive ingredients at 45 FR 20674 does not purport to be complete, suggested that binders, humectants, surfactants, and flavorants be added to the list.

As the comment noted, the types of inactive ingredients cited at 45 FR 20674 were intended as examples, not as a complete list. The agency believes that it is unnecessary to expand the list to include other examples of types of inactive ingredients.

8. One comment disagreed with the Panel's recommendation that a special panel is needed to review inactive ingredients in anticaries drug products. The comment stated that such ingredients are mostly found in cosmetics as well as drugs, and the current Cosmetic Ingredient Review sponsored by manufacturers of cosmetic products is fulfilling the need to examine more carefully the properties of certain ingredients.

The Panel stated that it did not undertake an extensive review of inactive ingredients because many of these ingredients are used in the formulation of many drug products other than those reviewed by the Panel. The Panel felt that it was not appropriate that inactive ingredients, except for abrasives, be dealt with specifically and solely in relation to dentifrices and dental care agents. Thus, the Panel recommended that the safety and the advisability of including specific inactive ingredients in drug products should be reviewed by an appropriate panel (45 FR 20674). The agency does not plan to establish a special panel to review inactive ingredients as part of the OTC drug review. The agency is aware of the Cosmetic Ingredient Review, which is a voluntary, industry-sponsored review to determine those cosmetic ingredients for which there is a reasonable certainty in the judgment of competent scientists that the ingredient is safe under its conditions of use (Ref. 1). Tentative and final reports on the ingredients reviewed are publicly available. The reports on inactive ingredients resulting from the Cosmetic Ingredient Review may be applicable to inactive ingredients used in OTC drug products, and the agency will consider these reports, as applicable, should questions arise regarding the presence of these inactive ingredients in OTC drug products. Under 21 CFR 330.1(e), an OTC drug product must contain only suitable inactive ingredients which are safe in the amounts administered and do not interfere with the effectiveness of the preparation or with suitable tests or assays to determine if the product meets

its professed standards of identity, strength, quality, and purity.

Reference

(1) Cosmetic Ingredient Review Procedures, Cosmetic Ingredient Review, 1110 Vermont Ave. NW., Washington, DC 20005.

9. One comment objected to the inclusion of 6 percent alcohol in a marketed 0.05-percent sodium fluoride dental rinse. The comment stated that the inclusion of alcohol in such products is unnecessary, that fluoride dental rinses employed in anticaries effectiveness studies did not contain alcohol, and that "it is generally accepted by the dental profession that daily rinses (containing alcohol) can be harmful to oral health, if continued over long periods." The comment urged FDA to take action against the inclusion of alcohol in fluoride dental rinses.

The OTC drug review regulations state that OTC drug products should contain "only suitable inactive ingredients which are safe in the amounts administered and do not interfere with the effectiveness of the preparation. . . ." (21 CFR 330.1(e)). The Panel considered alcohol to be an inactive ingredient in anticaries drug products containing fluoride (45 FR 20670) and did not take a position as to its value as an inactive ingredient in anticaries drug products or indicate that its presence in such drug products decreases their effectiveness. Although the Panel noted that inactive ingredients can have an irritating effect on the oral mucosa (45 FR 20674), it did not specifically indicate that such problems arise with daily use of dental rinses containing alcohol. The agency is unaware of significant reports of irritation or other adverse reactions due to fluoride dental rinse products containing 6 percent alcohol or of data that indicate that the presence of alcohol decreases the effectiveness of such products.

the Advisory Review Panel for OTC Oral Cavity Drug Products reviewed mouthwash drug products that contain alcohol and have antimicrobial claims and reviewed ethyl alcohol specifically as an antimicrobial active ingredient in mouthwashes (47 FR 22811–22873). That Panel recommended that ethyl alcohol be Category III as an antimicrobial mouthwash based on insufficient evidence of effectiveness, but stated that ethyl alcohol is safe for this use. Although the Oral Cavity Panel did not propose an antimicrobial mouthwash dosage for ethyl alcohol, it discussed concentrations well above 6 percent (i.e., 35 to 70 percent) for mouthwash use and noted that alcohol has been used safely in mouthwash products for many years (47 FR 22872).

The comment did not present any data or information to support its statement that the dental profession generally considers the daily use of mouthrinses containing alcohol harmful to oral health if continued over long periods or to demonstrate that daily rinsing over long periods with a product containing 6 percent alcohol is harmful to oral health. Therefore, the agency has no basis at this time for excluding alcohol as an inactive ingredient in fluoride dental rinse drug products.

10. A number of comments objected to the Panel's discussion of the relationship between sugar consumption and dental caries, and its recommendation that all processed foods be labeled with their percentage of sucrose and total monosaccharide and disaccharide content (45 FR 20672). The comments argued that the Panel had exceeded the scope of its authority by including this topic in its report. Some of the comments denied the primary importance of sugar in the etiology of dental caries and submitted data and cited numerous references to support their position (Refs. 1 and 2). One comment requested that the preamble to the tentative final monograph contain an explicit statement disavowing the Panel's conclusions on the etiology of dental caries and its recommendations on food labeling.

While the agency appreciates the Panel's concern with the etiology of dental caries, the Panel's comments concerning the role of sugar in the etiology of dental caries and the Panel's recommendation for mandatory labeling of sugar content on processed foods are outside the scope of the OTC drug review and thus will not be addressed in this tentative final monograph.

References

(1) Comment No. C00020, Docket No. 80N–0042, Dockets Management Branch.

(2) Comment Nos. C00011, C00017, and C00023, Docket No. 80N–0042, Dockets Management Branch.

11. One comment pointed out that the phrase "with an additive" was omitted from the Panel's statement at 45 FR 20672 concerning the caries-incidence liability of chewing gum. The comment indicated that the statement should read: "With reference to recommendation (4), the Panel believes that the evidence at this time is insufficient to allow any gum with an additive (on the market or proposed) to make the claim, 'does not promote tooth decay'."

The agency believes that, in the context of the Panel's discussion, the Panel intended the meaning conveyed by the comment's revised sentence.

B. Comments on the Switch of Prescription Anticaries Drug Products to OTC Status

12. A number of comments supported the Panel's recommendation that certain fluoride dental rinses and gels be switched from prescription to OTC status to aid in the prevention of dental caries. One comment, however, expressed concern that "people think if something is good, more is better. This is a bad idea since fluoride is a dangerous chemical and should be kept on a prescription basis."

The agency agrees with the Panel's recommendation to switch certain fluoride rinses and gels from prescription to OTC status. The benefits of having these anticaries products available OTC far outweigh the minimum risk involved. (See comment 13 below). Further, the Panel's recommended package size limitation and the labeling warnings and directions are sound control measures against potential misuse. The comment did not submit any data to support its statement that consumers will use excessive quantities of these products.

13. Several comments responded to FDA's request for comments and data on the issue of whether fluoride gels and rinses provide any added benefit to persons who also use a fluoride dentifrice daily, who live in areas where optimal levels of fluoride (i.e., approximately 1 part per million (ppm)) are present in the water supply, and who may also be given professionally applied fluoride treatments periodically.

One comment stated that the Council on Dental Therapeutics of the ADA has reviewed clinical studies that indicate that daily use of a 0.05-percent sodium fluoride rinse provides a reduction in caries that is additive to the daily use of a fluoride dentifrice and to water fluoridation. However, the clinical studies were not cited by the comment. another comment submitted a list of references on the topical application of fluoride and the use of fluoride rinses (Ref. 1). The comment, from a dentist, reported from personal experience that daily 0.05 percent sodium fluoride rinses were more effective than weekly 0.2 percent sodium fluoride rinses and concluded that the frequency of use of rinses is very important. The comment recommended a twice-daily use of a neutral sodium fluoride rinse. One comment stated that evidence in the literature shows that fluoridated water reduces dental caries by approximately 65 percent, whereas fluoride dentifrices

reduce them by approximately 35 percent. No supporting data were submitted by the comment.

One comment submitted a 30-month clinical study by Triol et al. (Ref. 2) conducted on schoolchildren (mean age 11.5 years) who lived in an area without optimal water fluoridation. The study was conducted to determine the additive caries-reducing effect obtained from the daily supervised use at school of a dentifrice containing 0.76 percent sodium monofluorophosphate and mouthrinses containing sodium flouride at 0.025, 0.05, and 0.1 percent concentrations. A nonfluoride mouthrinse was used as a contol. The study results showed that after 30 months, the use of each sodium flouride mouthrinse concentration combined with the sodium monofluorophosphate dentifrice reduced cavities when compared with the combined use of the sodium monofluorophosphate dentifrice and the control mouthrinse. Children who used a 0.025-percent and a 0.1-percent sodium fluoride mouthrinse with the fluoride dentifrice developed 9.2 and 7.8 percent fewer decayed, missing, and filled teeth, respectively, than did children who used a nonfuoride rinse. Daily use of the 0.05-percent sodium fluoride mouthrinse (the concentration recommended for OTC use by the Panel) produced modest additional benefits when used with fluoride dentifrice toothbrushing. Children in this group developed 11.1 percent fewer decayed, missing, and filled tooth surfaces during the 30-month evaluation period than children who used a nonfluoride rinse. Nearly the entire benefit resulted from a reduction in caries in interproximal (between-the-teeth) tooth surfaces. Because reduction of dental caries from the use of fluoride rinses results from the presence of the fluoride ion, the agency believes it is likely that similar findings would be produced by the use of gels or rinses containing other fluoride salts, such as stannous fluoride or acidulated phosphate fluoride, with the same concentration of fluoride.

The agency has reviewed other studies in which combinations of fluoride agents and methods have been used. Horowitz (Ref. 3) points out that there is increasing evidence that various combinations of fluoride agents produce additive anticariogenic effects. Although the mechanisms by which fluorides prevent dental caries are not fully understood, they probably vary, depending upon the agent used, its route of administration, its concentration, its frequency of use, the vehicle used to deliver it, and the age of the person who receives it (Refs. 4, 5, and 6). Several mechanisms may operate simultaneously, with one or another preeminent at different times because of local conditions at the tooth surface. It is thus logical to expect added benefits to accrue from the use of combinations of fluoride agents and methods, particularly those with different mechanisms of action.

Because the Triol study (Ref. 2) was intentionally done in a community where the drinking water contained less than 0.3 ppm of fluoride, it provides no information on additive benefits from the use of fluoride rinses in a community with a fluoridated water supply. However, at least three other studies strongly suggest that such benefits occur (Refs. 7 through 10). Driscoll et al. (Refs. 7 and 8) conducted a study on schoolchildren (mean age 12.8 years) who lived in a community with an optimally fluoridated water supply and used either 0.2 percent sodium fluoride rinse once a week or 0.05 percent sodium fluoride rinse once a day. A control group of children used a placebo rinse once a week. The 18-month interim results and 30-month final results of this study showed that both 0.2 percent and 0.05 percent sodium fluoride rinse solutions effectively reduced the incidence of dental caries. These reductions in caries were in addition to those already accrued from consuming optimally fluoridated drinking water.

It is likely that most of the children who participated in the study by Driscoll et al. (Refs. 7 and 8) were also using a fluoride-containing dentifrices at home. Because fluoride dentirfrices account for about 85 percent of all "toothpaste" sales, that assumption is reasonable. Therefore, in that study, the school-based daily and weekly fluoride mouthrinsing regimens may be regarded as being effective in reducing dental decay among children who live in a community with a fluoridated water supply and, for the most part, use a fluoride-containing toothpaste.

Kawall et al. (Ref. 9) conducted a 2-year study on schoolchildren (initially 9 years of age) who resided in an area with an optimally fluoridated water supply and used a 0.2-percent sodium fluoride rinse once a week. A control group of children was also included in the study. Results after 2 years showed that the fluoride rinse group had a 33.8-percent greater caries reduction than the control group. Radike et al. (Ref. 10) conducted a study on schoolchildren (8 to 13 years of age) who resided in a community with a fluoridated water supply and used a 0.1-percent stannous fluoride rinse once a day for 2 school years. A control group of children was also studied. After 2 years, two examiners independently observed caries reductions of 33 percent and 43 percent in decayed, missing, anf filled tooth surface scores for the group using the stannous fluoride rinse as compared with the control group. These studies show that mouthrinsing with flouride solutions, either daily or weekly as appropriate, provides additional protection against dental decay for persons living in a community with a fluoridated water supply.

As mentioned by one comment, the Council on Dental Therapeutics of the ADA recognizes the value of daily and weekly fluoride mouthrinsing for caries prevention in communities with fluoridated water (Ref. 11). Additionally, another ongoing study shows that children in an area without fluoridated water who rinse their mouth weekly in school with 0.2 percent sodium fluoride, ingest a tablet containing 1 mg of fluoride on school days, and receive fluoride dentifrice and toothbrushes for toothbrusing at home, demonstrate a pronounced reduction in dental decay (Refs. 12 through 15). After 8 years of this program, children 6 to 14 years of age in the program had 49 percent less dental decay than children of the same ages in the same area who had not participated in the program. Decay in mesiodistal tooth surfaces was lower by a striking 86 percent (Ref. 15).

Because rinsing daily with 0.05 percent sodium fluoride is at least as effective as weekly rinsing with 0.2 percent sodium fluoride, the agency concludes that the use of fluoride rinse concentrations combined with other fluroide programs is beneficial in reducing dental decay. Based on the cited studies, the agency concludes that beneficial additive effects occur from the combined use of fluoride rinses or gels and fluoride dentifrices in communities with either a fluoridated or nonfluoridated water supply. Therefore, in order to inform consumers that a decrease in the incidence of dental decay can result from the combined use of fluoride from different sources, the agency is proposing that the following statement be included under "Optional additional labeling statement" in § 355.50(f): "The combined daily use of a fluoride treatment" (select one of the following: "rinse" or "gel") "and a fluoride toothpaste can aid in reducing the incidence of dental cavities."

References

(1) Comment C00005, Docket No. 80N-0042, Dockets Management Branch.

(2) Triol, C. W., et al., "Anticaries Effect of a Sodium Fluoride Rinse and an MFP Dentifrice in a Nonfluoridated Water Area: A

Thirty-month Study," *Clinical Preventive Dentistry,* 2:13–15, 1980.

(3) Horowitz, H. S., "Combinations of Caries-preventive Agents and Procedures," *Journal of Dental Research,* 59:2183–2189, 1980.

(4) Brown, W. E., et al., "Effects of Fluoride on Enamel Solubility and Cariostasis," *Caries Research,* 11:118–141, 1977.

(5) Ericsson S. Y., "Cariostatic Mechanisms of Fluorides: Clinical Observations," *Caries Research,* 11:2–41, 1977.

(6) Mellberg, J. R., "Enamel Fluoride and its Anticaries Effects," *Journal of Preventive Dentistry,* 4:8–20, 1977.

(7) Driscoll, W. S., et al., "Caries-preventive Effects of Daily and Weekly Fluoride Mouthrinsing in an Optimally Fluoridated Community: Findings After Eighteen Months," *Pediatric Dentistry,* 3:316–320, 1981.

(8) Driscoll, W. S., et al., "Caries-preventive Effects of Daily and Weekly Fluoride Rinsing in a Fluoridated Community: Final Results After 30 Months," *Journal of Dental Association,* 105:1010–1013, 1982.

(9) Kawall, K., et al., "The Effect of a Fluoride Mouthrinse in an Optimally Fluoridated Community—Final Two Year Results," (abstract 646), *Journal of the American Dental Research,* 60:471, 1981.

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

(11) Council on Dental Therapeutics, "Accepted Dental Therapeutics," 39th Ed., American Dental Association, Chicago, p. 352, 1982.

(12) Horowitz, H. S., et al., "Evaluation of a Combination of Self-Administered Fluoride Procedures for Control of Dental Caries in a Non-Fluoride Area: Findings After 2 Years," *Caries Research,* 11:178–185, 1977.

(13) Horowitz, H. S., et al., "Evaluation of a Combination of Self-administered Fluoride Procedures for the Control of Dental Caries in a Nonfluoride Area: Findings After Four Years," *Journal of the American Dental Association,* 98:219–223, 1979.

(14) Horowitz, H. S., et al., "A Program of Self-Administered Fluorides in a Rural School System," *Community Dental Oral Epidemiology,* 8:177–183, 1980.

(15) Horowitz, H. S., et al., "Eight-year Evaluation of a Combined Fluoride Program in a Non-fluoride Area," (abstract 915), *Journal of Dental Research,* 61:280, 1982.

14. One comment stated that the Panel should have included systemic fluoride preparations among the Category I anticaries drug products because there is adequate experimental evidence supporting the effectiveness of systemic fluorides and because concern over toxicity could be handled by limiting the maximum amount of fluorine per package as has been done in the case of other fluoride-containing products. The comment contended that making systemic fluoride products available OTC could make it possible for a large segment of the population to enjoy the anticaries benefits of such products and urged the Panel to include systemic fluoride preparations in its review.

The agency did not include systemic fluoride preparations in the call-for-data notice for dentifrices and dental care drug products (38 FR 2781). No data on systemic fluorides were submitted to the Panel for review.

The Council on Dental Therapeutics of the ADA advises against the unrestricted distribution of systemic fluoride preparations (Ref. 1), and the agency concurs. Systemic fluoride preparations are usually prescribed for young children who live in areas where water supplies are deficient in fluorides. The ADA states that the ingestion of systemic fluoride preparations in addition to ingesting fluoridated water does not provide an additional substantial reduction in caries prevalence for adults or children, but may produce fluorosis in developing teeth of young children (Ref. 1).

Fluoridation of public water supplies has been safely and effectively used for many years to provide optimal levels of the fluoride ion to large segments of the population (Ref. 1). The optimal range of fluoride in drinking water to prevent caries is from 0.7 to 1.2 ppm. The need for additional systemic fluoride for any child depends on the fluoride concentration in drinking water and the age of the child (Ref. 1). Thus, professional supervision in the use of systemic fluoride preparations is necessary to assure that they are safely and effectively used. Although, as the comment points out, the maximum amount of fluoride per container could be limited to increase the safety of these products, consumers may not be aware of the extent to which their water supply is fluoridated and, therefore, may lack adequate knowledge to use systemic fluoride drug products effectively. Consequently, in this tentative final monograph the agency is not proposing labeling intended to inform consumers about the use of systemic fluorides.

However, the agency recognizes that Category I dental rinses have been used as fluoride supplements for ingestion in addition to their use as topical rinses. The ADA recommends a daily dosage of 2.2 mg sodium fluoride or 1 mg fluoride ion as a supplement for children 3 to 13 years of age in an area with less than 0.3 ppm in the water supply and 0.5 mg fluoride ion as a supplement for children 3 to 13 years of age in an area with between 0.3 to 0.7 ppm in the water supply (Ref. 1).

The agency concurs with the ADA's recommended dosage. The agency has determined that 5 milliliters (mL) of 0.02 percent or 10 mL of 0.01 percent flouride ion rinses included in the tentative final monograph will provide approximately 1 mg of fluoride ion and that 2.5 mL of 0.02 percent or 5 mL of 0.01 percent fluoride rinses will provide approximately 0.5 mg of fluoride ion. The agency concludes that systemic use of fluoride rinses as a supplement should be under professional supervision and is therefore including the following directions for use of these rinses as supplements in the professional labeling section of the tentative final monograph based on the ADA's dosage recommendations: Children 3 to under 14 years of age: as a supplement in areas where the water supply is nonfluoridated (less 0.3 part per million), clean the teeth with a toothpaste and rinse with 5 milliliters of 0.02 percent or 10 milliliters of 0.01 percent fluoride ion rinse daily, then swallow. When water supply contains 0.3 to 0.7 part per million fluoride ion, reduce the dose to 2.5 milliliters of 0.02 percent or 5 milliliters of 0.01 percent fluoride ion rinse daily.

Reference

(1) Council on Dental Therapeutics, "Accepted Dental Therapeutics," 39th Ed., American Dental Association, Chicago, pp. 344–368, 1982.

15. One comment requested that a neutral 0.2-percent sodium fluoride dental rinse be allowed to be marketed OTC. The comment explained that two programs in California enable elementary school children to participate in a weekly dental rinse program using 0.2 percent sodium fluoride. The comment pointed out, however, that California law requires that a dentist, physician, or pharmacist mix the 0.2-percent sodium fluoride solution, and, consequently, dentists participating in the program must spend much of their time mixing solutions rather than conducting dental screenings and providing dental education.

The agency understands that the technical aspects involved in mixing the 0.2-percent fluoride rinse are time-consuming and commends the comment's desire for dentists to devote more time to the dental care of school children. However, at this time, the agency is not aware of any data to show that a 0.2-percent sodium fluoride dental rinse, currently marketed by prescription only, can be safely marketed OTC. The Panel reviewed a number of studies attesting to the safety and effectiveness of a 0.05-percent sodium fluoride solution used daily as a rinse (45 FR 20686–20687) and, based on these data, recommended that the 0.05-percent sodium fluoride solution be switched from prescription to OTC marketing status. Without safety data for the 0.2-percent sodium fluoride dental rinse, the agency has no basis for granting the comment's request.

C. Comments on Specific Anticaries Active Ingredients

16. Several comments objected to the Panel's discussion of the claim "does not promote tooth decay" and to the Panel's recommendation that the evidence at this time is insufficient to allow any sucrose-containing chewing gum to make this claim (45 FR 20672). The comments pointed to the Panel's statement that during the Panel deliberations the Bureau of Drugs (now the Center for Drugs and Biologics) decided that products making noncariogenic claims (such as "does not promote tooth decay") should be reviewed by the Bureau of Foods (now the Center for Food Safety and Applied Nutrition) because noncariogenic claims are not considered drug claims (45 FR 20669). Two comments (Refs. 1 and 2) argued that the Panel's recommendation on noncariogenic claims was thus extraneous to this OTC drug rulemaking and should be deleted, along with certain portions of the Panel's discussion about the cariogenicity of foods (45 FR 20672).

The chairman of the Dental Panel requested that two paragraphs be added to the report stating that the Panel had discussed at length the action of ingredients designed to negate the cariogenic effects of sugars. The chairman commented that the Panel had concluded that dicalcium phosphate dihydrate is safe, but that an additional clinical study would be needed to prove effectiveness (Ref. 3).

Some comments also objected to the Panel's classification of phosphates, including dicalcium phosphate dihydrate and calcium sucrose phosphate, in Category II as anticaries agents (45 FR 20689). One comment stated that phosphate compounds are chemical additives to foods and should not be included in the proposed OTC monograph. Another comment contended that calcium phospate dihydrate and calcium sucrose phosphate have a history of safe use. According to the comment, this Category II classification contradicts a Department of Commerce report prepared by the Federation of American Societies of Experimental Biology which states that phosphates, especially calcium phosphates, are safe as food ingredients (Ref. 4). The comment also pointed out that many of the phosphates are on the GRAS list (food substances generally recognized as safe). The comments argued that a Category III classification (based on insufficient effectiveness data) for these phosphate ingredients would be more appropriate than the Panel's Category II classification (Refs. 4 and 5).

The agency agrees that noncariogenic claims (such as "does not promote tooth decay") are not drug claims. Of course, any noncariogenic claims made on food product labeling must not be false or misleading. However, these claims will not be reviewed as part of this OTC drug rulemaking. As the Panel chairman has pointed out, the Panel spent a considerable amount of time during its deliberations discussing the role of sugar in dental health and the action of substances intended to negate the cariogenic effects of sugars. The Panel report does include a discussion of the Panel's views on these issues; however, the agency will not delete or add segments to the Panel's report as requested by the comments.

The Panel placed phosphates in Category II as anticaries agents (i.e., ingredients which aid in the prevention of dental cavities) based on lack of marketing and on lack of evidence of effectiveness (45 FR 20689). Calcium phosphate (mono-, di-, and tribasic) is listed in 21 CFR 182.1217 as a multiple purpose GRAS food substance. In the **Federal Register** of December 18, 1979 (44 FR 74845), FDA proposed to affirm that dicalcium phosphate is generally recognized as safe as a direct food ingredient under certain conditions. Although phosphates have been added to foods, they have never been marketed as anticaries drug products. Therefore, they are not appropriately included in the OTC drug review program. Thus, the agency will not consider dicalcium phosphate dihydrate, calcium sucrose phosphate, or any other phosphate, in this OTC anticaries drug rulemaking. Any OTC anticaries drug product containing a phosphate as an active ingredient is a new drug as defined in 21 U.S.C. 321(p) and under 21 U.S.C. 355 may not be marketed without an approved new drug application.

References

(1) Comment C00021, Docket No. 80N-0042, Dockets Management Branch.
(2) Comment C00026, Docket No. 80N-0042, Dockets Management Branch.
(3) Comment C00002, Docket No. 80N-0042, Dockets Management Branch.
(4) Comment C00029, Docket No. 80N-0042, Dockets Management Branch.
(5) Comment C00024, Docket No. 80N-0042, Dockets Management Branch.

17. One comment contended that the Panel's listing of hydrogen fluoride as an inactive ingredient (45 FR 20670) was misleading. The comment stated that, although no marketed product contains hydrogen fluoride as its sole anticaries ingredient, in a proper formulation this ingredient would be active against caries because hydrogen fluoride readily yields ionic fluoride in solution.

The agency agrees that hydrogen fluoride, in an appropriate formulation, could be considered an active anticaries ingredient and recognizes that a marketed product containing hydrogen fluoride as an active ingredient in combination with sodium fluoride, available only by prescription, was submitted to the Panel for review (Refs. 1 and 2). The product is a dental rinse containing the ingredients sodium fluoride and hydrogen fluoride, buffered to pH 3, with an effective fluoride ion concentration of 1.23 percent. In this formulation hydrogen fluoride contributes approximately 50 percent of the total fluoride ion content, and sodium fluoride contributes the other 50 percent. The agency is unable to ascertain why the Panel classified the ingredient hydrogen fluoride as inactive and why it did not classify in its report the combination dental rinse containing hydrogen fluoride and sodium fluoride. It is possible that the Panel did not classify the product based on the manufacturer's statement in its submission that "we do not believe that this product can or should be considered in the Over-the-Counter (OTC) category. It is intended and sold for use only by the dental profession . . . ." It is also possible that the Panel may have considered the hydrogen fluoride present in the product as a pharmaceutic aid to adjust the acidity (pH).

A dental rinse containing ionic fluoride derived from hydrogen fluoride in an appropriate formulation that is similar to the Category I acidulated phosphate fluoride dental rinse formulation with an effective fluoride ion concentration of 0.02 percent may be safe and effective as an OTC anticaries drug product. However, such a product with an appropriate formulation was not submitted to the Panel or to the agency.

The Panel recommended specific formulation parameters (buffers, pH, and the effective fluoride ion concentration) for the Category I acidulated phosphate fluoride rinse in § 355.10(b)(1) of its recommended monograph because of the importance of these parameters in defining a safe and effective fluoride dental rinse (45 FR 20685, 20686, and 20690). The agency believes that specific parameters would be equally important to define the formulation for a rinse containing ionic fluoride derived from hydrogen fluoride, particularly in view of the fact that hydrogen fluoride as an unbuffered single active ingredient is an extremely

irritating, corrosive, and toxic chemical (Ref. 2).

The agency is therefore proposing a Category III classification for a fluoride dental rinse containing ionic fluoride derived from hydrogen fluoride in an appropriate formulation at an acceptable fluoride ion concentration (0.02 percent) in this tentative final monograph.

References

(1) OTC Volum 080012.

(2) Windholz, M., editor, "The Merck Index," 10th Ed., Merck and Co., Rahway, NJ, pp. 695–696, 1983.

D. Comments on Dosages for OTC Anticaries Drug Products

18. One comment stated that the directions for use of anticaries dentifrices need not specify either a minimum or a maximum dose, as recommended by the Panel (45 FR 20674), because the user has no means of determining the weight or the volume of a dose of dentifrice. The comment added that the clinical determinations of effectiveness have almost invariably been made according to the user's ad libitum application of dentifrice to the toothbrush.

The Panel's statement at 45 FR 20674 was as follows:

> The label [of an OTC anticaries drug product] should include a clear statement of the usually effective minimum and, where applicable, maximum doses [or concentration if more appropriate] per time interval. . . . The Panel will recommend specific directions for use under each drug statement in later sections of this document.

The Panel's statement apparently was intended as a general, not a specific, recommendation because, in its recommended directions for use in § 355.50(d)(1) of its monograph, the Panel did not specify a minimum or a maximum dose for anticaries dentifrices. The Panel recommended that consumers brush their teeth thoroughly at least once daily or as directed by a dentist or physician, without specifying any quantity of dentifrice to be used. Thus, the comment and the Panel are in agreement. The agency is proposing directions for use as recommended by the Panel.

19. One comment requested that the monograph provide for the marketing of a sodium fluoride dental rinse concentrate which, when diluted with water, would provide an aqueous solution containing 0.05 percent sodium fluoride. The comment explained that as marketed in the undiluted, concentrated form, the level of sodium fluoride in the product would exceed the Panel's recommended 0.05 percent concentration, but the total fluorine content of the product would not exceed the Panel's recommended limitation of 120 mg total fluorine. The comment noted that the Panel's recommended monograph allows marketing of a powder or effervescent tablet form of stannous fluoride which, when mixed with water according to the product's directions for use, results in a 0.1-percent stannous fluoride solution. The comment stated that there appears to be no valid reason why a concentrated dental rinse bearing adequate directions for mixing with water to produce a 0.05-percent sodium fluoride aqueous solution should be treated differently from a similar stannous fluoride dental rinse "concentrate."

The agency agrees with the comment that a sodium fluoride dental rinse concentrate can be marketed OTC provided the product is clearly labeled as a concentrate, adequate directions for the proper dilution of the product to a 0.05-percent solution are clearly stated, and the package does not contain more than 120 mg total fluorine. Therefore, the agency is proposing that the anticaries active ingredient statement in § 355.10(b)(3) be revised to include a sodium fluoride dental rinse concentrate as follows: Sodium fluoride concentrate containing adequate directions for mixing with water before using to result in a 0.02-percent or 0.05-percent aqueous solution with a pH of approximately 7. Concentrates can be marketed as solutions, powders, or tablets; and the agency is proposing that the statement of identity include terms that describe these concentrated product forms. (See comments 25 and 26 below.)

In order to alert consumers that dental rinse products in concentrated form (solutions, powders, and effervescent tablets) must be diluted or dissolved in water before using, the agency is proposing the following warning for these dosage formulations: "Do not use before mixing with water. Read the directions carefully."

Based on § 355.10(b)(5) of the Panel's recommended monograph, the agency is also proposing that stannous fluoride may be marketed as a dental rinse in concentrated form to be mixed with water immediately before using, provided it is marketed in a stable form (such as effervescent tablets, powders, or in a nonaqueous solution (e.g., anhydrous glycerin)). The labeling requirements proposed in this document for sodium fluoride concentrates (i.e., statement of identity, warnings, and directions) are also applicable to and are proposed for stannous fluoride concentrates.

20. Noting the Panel's recommendations to make low-fluoride dentifrices available OTC, one comment requested that FDA determine what higher levels of fluoride concentration now become appropriate for dispensing on prescription or for use only under professional surveillance.

The Panel recommended that certain fluoride dental rinses and gels that have previously been restricted to prescription use be made available OTC, provided that they contain no more than 120 mg total fluorine per package (45 FR 20666). This rulemaking proceeding for OTC anticaries drug products establishes which anticaries drugs are generally recognized as safe and effective for OTC use and the concentration or dosage at which they can be safely used OTC. Fluoride concentrations higher than those established in the final monograph are intended for use only under professional supervision. This OTC drug rulemaking proceeding is not the appropriate forum for determining what these higher levels are. If a manufacturer wishes to market a prescription product with a higher fluoride concentration, the manufacturer must file an NDA to obtain appropriate approval.

21. One comment requested that a 0.02-percent sodium fluoride acidulated phosphate fluoride dental rinse formulation and a 0.02-percent sodium fluoride neutral (nonacidulated) dental rinse formulation be classified as Category I OTC anticaries drug products based on data that were submitted to the Panel but, due to an oversight, were not reviewed (Refs. 1 and 2). The comment also submitted additional data to the agency (Refs. 3 through 6). The comment recommended that the directions for use of these products state that adults and children 6 years of age and older should rinse twice daily with 10 mL of a 0.01-percent fluoride ion solution for 30 seconds or 60 seconds.

The agency has reviewed the available data and tentatively determined that it supports a Category I classification for 0.02 percent sodium fluoride (0.01 percent fluoride ion) in an acidulated phosphate fluoride dental rinse and for 0.02 percent sodium fluoride in a neutral dental rinse (pH of approximately 7).

The agency's tentative decision to place 0.02 percent sodium fluoride in an acidulated phosphate fluoride dental rinse in Category I is based on one published and two unpublished controlled double-blind clinical studies that demonstrate a significant reduction of caries in children who used this dental rinse. A 26-month study by Finn

et al. (Ref. 7) included 593 children; 453 children completed the clinical trial. There was a significant reduction in caries for those children who rinse twice daily with either one of the acidulated phosphate fluoride dental rinses containing 0.01 percent or 0.02 percent fluoride ion at pH 3.5 twice daily when compared with the children who rinsed with the placebo twice daily ($p<0.05$). No statistically significant differences resulted between 0.01 percent and 0.02 percent acidulated phosphate fluoride ion rinses ($p<0.05$).

A 37-month unpublished study (Ref. 1) included 817 children; 523 children completed the clinical trial. There was a significant reduction in caries for those children who had rinsed with 0.02-percent sodium fluoride in an acidulated phosphate fluoride dental rinse at pH 3.5 when compared with the children who rinsed with the placebo ($p<0.05$).

A 24-month unpublished study (Ref. 1) included 1,214 children; 817 children completed the clinical trial. There was a significant reduction in caries for those children who rinsed with either one of the acidulated phosphate fluoride dental rinses containing 0.01 percent or 0.02 percent fluoride ion at pH 3.5 when compared with the children who rinsed with the placebo ($p<0.05$).

The agency's tentative decision to place 0.02 percent sodium fluoride in a neutral dental rinse (pH of approximately 7) in Category I is based on one unpublished in vitro study and two published clinical studies (Refs. 3, 4, and 5). The unpublished study contains in vitro data concerning the effect of a neutral 0.02=percent sodium fluoride dental rinse on sound and presoftened human enamel using the Intraoral Caries Test System (Ref. 3). These data demonsrate an increased fluoride uptake with the neutral sodium fluoride rinse when compared with a placebo.

The study by Englander et al. (Ref. 4) concerns the effectiveness of 1.1 percent sodium fluoride gels. Although the study does not provide specific information about the effectiveness of the 0.01-percent fluoride ion neutral dental rinse, it does compare similar fluoride dental products at pH 4.5 and 7, suggesting that pH is not a significant factor in determining the effectiveness of a fluoride anticaries product.

The study of Forsman (Ref. 5) supports the anticaries effectiveness of the 0.011-percent fluoride ion (0.025 percent sodium fluoride) neutral dental rinse by demonstrating that the twice-daily use of a weaker dental rinse (0.011-percent fluoride ion) is more effective in preventing caries when compared with the weekly use of a more concentrated dental rinse of 0.090 percent fluoride ion (0.2 percent neutral sodium fluoride). In addition, one comment from a dentist also reported that a 0.05-percent sodium fluoride rinse (weaker solution) proved to be more effective than the weekly use of a 0.2-percent rinse (Ref. 6). Forsman's study supports the dentists's finding that increased frequency of rinsing is a significant factor in a rinse's efficacy. Based upon the available data, frequent use of low concentration rinses is safe and as effective as less frequent use of higher concentration rinses.

It is well known that the availability of the fluoride ion is the major determining factor in the effectiveness of all fluoride anticaries dental products. The studies demonstrate that 0.01 percent fluoride ion in an acidulated phosphate rinse is equally available and equally effective in a neutral rinse. In addition, the Panel did not distinguish between the safety and effectiveness of acidulated (0.02 percent fluoride ion) and neutral dental rinses containing 0.022 percent fluoride ion derived from 0.05 percent sodium fluoride. It recommended that both the acidulated and neutral forms of these rinses be Category I. The studies indicate that the amount of available fluoride ion, rather than the difference in the pH of these rinses between pH 3 and pH 7, is the determining factor in the efficacy of these dental rinses.

The Panel recommended that 10 mL of a 0.02-percent acidulated phosphate fluoride ion (2 mg fluoride ion) with a pH of 3.0 to 4.5 or 10 mL of a 0.05-percent sodium fluoride aqueous solution with a pH of approximately 7 be used once daily as a rinse. The comment recommended that 10 mL of a 0.01-percent acidulated phosphate fluoride ion and a 0.01-percent neutral fluoride ion derived from sodium fluoride (1 mg fluoride ion) be used twice daily as a rinse. The total daily dosage recommended by the comment for the 0.01-percent rinse is equivalent to the total daily dosage recommended by the Panel for a 0.02-percent rinse, i.e., 2 mg fluoride ion daily. Therefore, the agency proposes the following directions for the 0.01-percent acidulated phosphate and neutral fluroide ion rinses: "Adults and children 6 years of age and older: use twice a day after brushing your teeth with a toothpaste. Vigorously swish 10 milliliters of rinse between your teeth for 1 minute and then spit out. Do not swallow the rinse. Do not eat or drink for 30 minutes after rinsing. Children under 12 years of age should be supervised in the use of this product. Children under 6 years of age: consult a dentist or doctor."

The agency's detailed comments and evaluation of the data are on file in the Dockets Management Branch (Ref. 8).

References

(1) OTC Volume 080135.

(2) OTC Volume 080136.

(3) Comment No. CP, Docket No. 80N-0042, Dockets Management Branch.

(4) Englander, H.R., et al., "The Clinical Anticaries Effect of Repeated Topical Sodium Fluoride Applications by Mouthpieces," *Journal of the American Dental Association*, 75:638–644, 1967.

(5) Forsman, B., "The Caries Preventing Effect of Mouthrinsing with 0.025% Sodium Fluoride Solution in Swedish Children," *Community Dental Oral Epidemiology*, 2:58–65, 1974.

(6) Comment No. C00005, Docket No. 80N-0042, Dockets Management Branch.

(7) Finn, S.B., et al., "The Clinical Cariostatic Effectiveness of Two Concentrations of Acidulated Phosphate-fluoride Mouthwash," *Journal of the American Dental Association*, 90:292–296, 1975.

(8) Letter from W.E. Gilbertson, FDA, to Joseph Clark, Warner-Lambert Company, coded LET008, Docket No. 80N-0042, Dockets Management Branch.

E. Comments on Labeling of Anticaries Drug Products

22. Two comments objected to the warning for dental rinses and gels recommended by the Panel in § 355.50(c): "Do not swallow. Developing teeth of children under 6 years of age may become permanently discolored if excessive amounts of fluoride are repeatedly swallowed." One comment stated that fluoride dental rinses should not be recommended for use by children under 6 years of age, because children in this age group are most prone to develop tooth discoloration. The comment added that when a dentist or physician recommends a fluoride rinse for a child under 6 years of age, specific use instructions are provided, thus making such a warning unnecessary. The comment stated that the phrase "excessive amounts are swallowed" would raise unnecessary concerns, because infrequent accidental swallowing of the recommended amount of fluoride used in mouthrinsing would not be expected to cause permanent tooth discoloration, and the phrase "permanently discolored" would excessively alarm parents and discourage rather than encourage use of the product. The second comment stated that the warning would give consumers the mistaken impression that fluoride gels and rinses are less safe than dentifrices. The comment recommended, instead, that the following statement appear in the directions for fluoride gels.

rinses, and dentifrices: "Do not swallow. Repeated swallowing of excessive amounts of fluoride by children under 6 may permanently discolor developing teeth."

Because fluoride dental rinses and gels are recommended only for use in adults and children 6 years of age and older, the agency believes that a warning about discoloration of developing teeth in children under 6 years of age is not needed on the OTC market package. However, the agency's proposed directions for dental rinses and gels state that a dentist should be consulted before using these products in children under 6 years of age.

The warning recommended by one comment is not needed for fluoride dental rinses and gels as stated above, nor is it needed for fluoride dentifrices because these products have a long history of safe use. Studies have shown that the amount of toothpaste swallowed by children, even those 3 to 6 years of age, is less than 0.5 gram (g) per brushing, which is well below a toxic range (45 FR 20682). However, the agency believes that it would be helpful to the consumer to include the statement "Do not swallow" in the directions for use of fluoride rinses and gels. Therefore, the agency is proposing that the directions for fluoride rinses and gels include the statement "Do not swallow the" (insert dosage form, "rinse" or "gel," as applicable).

23. Two comments urged that adequate warnings about the harmful effects of fluoride be included in the labeling of all dental drug products containing fluoride. The comments contended that such information is necessary because fluoride from toothpastes, gels, and rinses is absorbed into the body and accumulates in body tissues; that absorbed fluoride rapidly enters into the general circulation, resulting in high blood fluoride levels that pose a particular risk to the child who is allergic and otherwise intolerant to fluoride; and that nausea and vomiting may result in young children who swallow fluoride toothpaste or rinses. The comments submitted a number of references to support their contentions (Refs. 1 and 2).

The agency has reviewed the Panel's evaluation of the safety data on fluoride drug products as well as the Panel's recommended labeling of these products and concludes that the recommended labeling is adequate and that additional warnings are not necessary. The Panel considered both animal and human studies in determining the safety of fluorides used in anticaries drug products (45 FR 20682–20684) and evaluated the possibility that these products might cause adverse effects on teeth or cause irritation of the oral mucosa. Attention was given especially to information related to adverse drug effects in both adults and children (45 FR 20682). The metabolism of fluoride involves rapid absorption of 90 percent or more of soluble fluoride, with perhaps half this fluoride reappearing in the urine, and the rest stored in bone and teeth (Ref. 3). Urinary excretion is prompt and sensitive even to low doses of fluoride. There is no evidence that fluoride is stored in soft tissues.

The Panel reviewed a number of studies that have been conducted to determine the amount of fluoride ingested during toothbrushing with a fluoride-containing dentifrice (45 FR 20682). These studies, which utilized a variety of testing procedures, indicate that the majority of individuals, including children aged 3 to 6 years, swallow less than 0.5 g of toothpaste per brushing (Refs. 4 through 9). The greatest amount swallowed was reported as slightly over 1 g (Refs. 8 and 9). Studies by several investigators, however, showed the amount swallowed to be substantially less (Refs. 4 through 7). These amounts can be considered well below a toxic range. A study of recorded cases of acute fluoride poisoning indicate that a range of 5 to 10 g of sodium fluoride can be considered a lethal dose for a 70-kilogram (kg) man (45 FR 20682).

Dental fluorosis occurs only when excessive fluorides are ingested regularly during the period of tooth development (45 FR 20682). Although 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 indicate that the formative state of the teeth of children 6 years of age and older (excepting third molars) is too advanced to be affected by excessive daily fluoride ingestion (45 FR 20685). Although it is conceivable that a child under 6 years of age could, by swallowing excessive amounts of fluoride-containing toothpaste and consuming fluoridated water, 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 the extremely widespread use of fluoride-containing dentifrices for over 20 years.

Concerning allergy or intolerance to fluorides, CPSC stated in the Federal Register of November 26, 1980 (45 FR 78632) that there is a relatively low incidence of adverse reactions (about 1 percent) associated with normal dosages of sodium fluoride. These reactions, which include gastrointestinal hemorrhages, eczema, dermatitis, and urticaria type reactions, cease upon termination of sodium fluoride therapy. CPSC also noted that there is "no scientific rationale for predicting a greater incidence of adverse reactions in children, whether due to intolerance or other factors. In fact, human experience data and the medical literature indicate very few adverse reactions, particularly in children."

The agency concludes that the adverse reactions reported from studies in children, toxicity studies in animals, and other available data are not of a sufficiently serious nature or sufficient number to warrant additional warnings on harmful effects in the labeling of dental drug products containing fluoride. This conclusion is supported by the long history of safe use of fluoride dentifrices which the Panel believed precluded the need for warnings against unsafe use, side effects, and adverse reactions. The Panel recommended, and the agency is proposing in this tentative final monograph, that children under 6 years of age should be supervised in the use of anticaries dentifrice products. The agency is proposing labeling for fluoride dental rinses and gels for use only in adults and children 6 years of age and older. The labeling directions state that a dentist or doctor should be consulted before using these products in children under 6 years of age. The agency's proposed directions for fluoride dental rinses and gels also include the statement "Do not swallow the" (insert dosage form, "rinse" or "gel," as applicable). (See comment 22 above.) The agency believes that these specific directions for use of dentifrices, gels, and rinses are adequate and will result in the safe use of these OTC anticaries drug products.

References

(1) Comment No. C00022, Docket No. 80N–0042, Dockets Management Branch.

(2) Comment No. C00027, Docket No. 80N–0042, Dockets Management Branch.

(3) Dunning, J. M., "Principles of Dental Public Health," 2d Ed., Harvard University Press, Cambridge, MA, pp. 367–403, 1970.

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(5) Duckworth, R., and S. Joyston-Bechel, "The Distribution of Dentifrice Fluoride During and After Toothbrushing," *Advances of Fluorine Research*, 4:113–119, 1966.

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

(7) Glass, R. L., et al., "Fluoride Ingestion Resulting from the Use of a Monofluorophosphate Dentifrice by Children," *British Dental Journal*, 138:423–426, 1975.

(8) Hargreaves, J. A., G. S. Ingram, and B. J. Wagg, "A Gravimetric Study of the Ingestion of Toothpaste by Children," *Caries Research*, 6:237–243, 1972.

(9) Hargreaves, J. A., G. S. Ingram, and B. J. Wagg, "Excretion Studies on the Ingestion of a Monofluorophosphate Toothpaste by Children," *Caries Research*, 4:256–268, 1970.

24. One comment objected to the labeling statement for stannous fluoride rinses and gels recommended by the Panel in § 355.50(e)(2): "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." The commenter stated that no warning on staining is necessary for stannous fluoride gels because there have been no reports of discoloration in the more than 5 years that the commenter has marketed a 0.4-percent stannous fluoride gel, and because no warning on staining is required for a stannous fluoride dentifrice. No supporting data were submitted by the commenter. The commenter mentioned the Panel's discussion on stannous fluoride dentifrices, in which the Panel stated that 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 dentifrice formulations (45 FR 20685). The commenter contended that, because the amount of stannous ion in a gel and a dentifrice are the same and the mode of application (with a toothbrush) of both formulations is identical, there should be no warning on staining for stannous fluoride gels.

The majority of the studies that the Panel reviewed concerning the incidence and degree of staining of tooth surfaces from the use of stannous fluoride dealt with stannous fluoride dentifrices. The Panel found that the presence of the stannous ion in stannous fluoride dentifrices may cause some staining of plaque and debris accumulation on the teeth (45 FR 20685). After considering all the available data on staining caused by stannous fluoride, the Panel concluded that because stannous fluoride dentifrices had been marketed for a long time with little consumer complaint, the staining apparently was not a significant problem. The Panel, therefore, decided that a labeling statement regarding staining need not be included in the labeling of stannous fluoride dentifrices. However, the Panel recommended that stannous fluoride gels and rinses should bear a labeling statement regarding staining because they had been available only by prescription, and had no prior marketing history of consumer use and acceptance.

In the interest of consumer awareness, the agency believes that all stannous fluoride dental products (i.e., dentifrices, rinses, and gels) should bear the labeling statement regarding staining. Studies have shown that stannous fluoride, whether formulated as a dentifrice or rinse, causes staining of tooth surfaces. Comparisons between subjects who used a control dentifrice and a stannous fluoride dentifrice in a 3-year study showed that after 6 months, a higher incidence and more pronounced staining occurred in the stannous fluoride group (Ref. 1). Two different studies were conducted in subjects who used a control dentifrice, a stannous fluoride dentifrice, or a sodium monofluorophosphate dentifrice. The results of one study showed that, initially, the amount of brown stain on teeth was similar in all subjects, but the group using the stannous fluoride dentifrice had a significantly larger increase in staining during the 2-year study period ($p < 0.001$) than the groups using sodium monofluorophosphate or control dentifrices (Ref. 2). The second study was conducted over a 3-year period and showed that the sodium monofluorophosphate and control groups had a higher percentage of subjects completely free of staining than did the stannous fluoride group. The degree of staining was also greater in the stannous fluoride group. The results indicated that the high degree of brown-black staining was specifically due to the stannous flouride dentifrice (Ref. 3).

The agency is not aware of any controlled studies that evaluated staining caused by dental gels; however, it is very likely that staining would occur from the use of gels similar to that which occurs from the use of dentifrices. A 2-year study that was conducted using a stannous fluoride mouthrinse and a control mouthrinse showed that after 8 months, some yellow pigmentation was present on the teeth of children who exhibited poor oral hygiene. This stain occurred in both the control and stannous fluoride groups, but was somewhat more noticeable in the stannous fluoride group. The results of the 2-year examination were similar to the 8-month examination (Ref. 4). Although there are few studies on the incidence of staining with stannous fluoride rinses and gels, the agency believes that because stannous fluoride, the active ingredient, causes staining of teeth, the staining would occur whether the stannous fluoride product is formulated as a rinse, gel, or dentifrice. Additionally, because of the difference in the composition and use of dentifrices from that of rinses and gels, the agency believes that the incidence and degree of staining may be greater with stannous fluoride gels and rinses than with stannous fluoride dentifrices. A dentifrice contains an abrasive to help clean the teeth (and thus helps to remove plaque and stain); rinses and gels do not contain an abrasive. Dentifrices are brushed on the teeth and the mouth is usually rinsed with water after use. However, stannous fluoride gels and rinses are brushed on the teeth, or swished around in the mouth, and then remain on the teeth for one minute before being spit out. The mouth is not rinsed with water. The residue is left in the mouth and no food or drink is supposed to be taken for 30 minutes. Stannous fluoride gels and rinses would remain on the teeth for a longer time than stannous fluoride dentifrices.

It is believed that staining occurs when the stannous (tin) component of the compound reacts with oxygen and/or sulfur in dental plaque (Ref. 5). The amount of staining has been associated with the degree of oral hygiene of the individual, i.e., individuals with poor oral hygiene have a higher incidence of staining than those whose oral hygiene is good (Refs. 3, 6, and 7). Subjects with less than adequate toothbrushing skills had more tooth staining than those who were conscientious in their toothbrushing habits (Ref. 3). Thus, the importance of good toothbrushing techniques should be encouraged not only to promote good oral health, but also to prevent or lessen the occurrence of any tooth staining. The agency believes that consumers should be aware that staining of the teeth can be caused by stannous fluoride dentifrices, rinses, and gels, and that proper brushing or a dental prophylaxis should remove the stains. Therefore, the agency is proposing that the labeling statement "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," be included under "additional labeling statements" in this tentative final monograph and be applicable to all stannous fluoride dental products.

References

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Children." *British Dental Journal*, 123:40–48, 1967.

(2) Fanning, E. A., et al., "The Effects of Fluoride Dentifrices on the Incidence and Distribution of Stained Tooth Surfaces in Children," *Archives of Oral Biology*, 13:467–469, 1968.

(3) Naylor, M. N., and R. D. Emslie, "Clinical Testing of Stannous Fluoride and Sodium Monofluorophosphate Dentifrices in London School Children," *British Dental Journal*, 123:17–23, 1967.

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

(5) Muhler, J. C., "Stannous Fluoride Enamel Pigmentation—Evidence of Caries Arretsment," *Journal of Dentistry for Children*, 54:157–161, 1960.

(6) Horowitz, H. S., and S. R. Chamberlin, "Pigmentation of Teeth Following Topical Applications of Stannous Fluoride in a Nonfluoridated Area," *Journal of Public Health Dentistry*, 31:32–37, 1971.

(7) Hyde, E. J., and J. C. Muhler, "Pigmentation of Teeth Treated with Stannous Fluoride and its Association with Caries Incidence and Oral Hygiene," *Journal of the Canadian Dental Association*, 29:514–520, 1963.

25. One comment pointed out that some current dentifrice products containing abrasives are formulated so that they appear transparent or translucent and are called gels by the manufacturers. The comment contended that, because consumers are accustomed to calling these products "gels," this term should continue to be used for such products. Two comments suggested using the term "nonabrasive dental gel" in §§ 355.3(d), 355.10(c), 355.20(b), and 355.50(a), (d)(4), and (e)(1) and (2) in place of the term "dental gel" to reflect the intended use of the product more accurately and to eliminate the possibility of consumers confusing the product with an abrasive-containing gel dentifrice.

The agency agrees that currently marketed transparent or translucent dentifrice products that contain abrasives should be permitted to continue to identify themselves as a "gel" because this term is widely used and understood by consumers. However, the agency does not believe that the term "gel" needs to be included in the monograph to describe these dentifrice products. The agency is proposing the terms "toothpaste" or "dentifrice" as optional alternatives in the applicable statement of identity and believes these terms accurately reflect product identity and are recognized by consumers as referring to products used to clean the teeth. (See comment 26 below.)

Although the agency is concerned that consumers may not be able to distinguish between abrasive-containing "gel" dentifrices and nonabrasive dental gels based on the similar physical appearance of these products, it disagrees with the coment's recommendation to use the term "nonabrasive dental gel" in the statement of identiy, § 355.50(a), to differentiate between gel dentifrices, which contain abrasives, and dental gels, which do not contain abrasives. The meaning of "nonabrasive" and "abrasive" may not be clear to many consumers, and the term "abrasive" might even discourage some consumers from using dentifrices. The agency agrees that the Panel's recommended statement of identity for nonabrasive dental gels may be confusing to consumers, particularly in the context of the extensive use of the term "gel" to describe abrasive-containing toothpastes. The agency also recognizes that nonabrasive dental gels have not been widely marketed and that consumers are not familiar with the use of the term "dental gel" to identify such products. The agency is therefore proposing to revise the statement of identity for nonabrasive dental gels to read: (select one or both of the following: "anticavity" or "fluoride") "treatment gel," in this tentative final monograph. In addition, the agency believes that the labeling statement proposed for nonabrasive dental gels in § 355.50(e)(1) of this tentative final monograph, "This is a(n) (select one or both of the following: "anticavity" or "flouride") "treatment gel, not a toothpaste. Read directions carefully before using," will also help consumers to clearly distinguish between a gel dentifrice and a nonabrasive dental gel. (See comment 36 below).

As for the comments' suggestion to use the term "nonabrasive dental gel" in the definition in § 355.3(g) and in the headings in §§ 355.10(c), 355.20(b), and 355.50(d) and (e), the agency has replaced the term "dental gel" with the term "treatment gel" throughout the monograph in the headings to be consistent with the statement of identity for these drug products.

26. One comment requested use of the term "fluoride" as an optional alternative to "anticavity," and the term "toothpaste" as an optional alternative to "dentifrice" in the labeling of anticaries drug products, because these terms most clearly reflect product identity and are well recognized by consumers.

The agency agrees with the comment that the terms "fluoride" and "toothpaste" accurately reflect product identity and are terms that are recognized by consumers. Accordingly, these terms are included as optional alternatives in the statement of identity proposed in § 355.50(a) of the tentative final monograph as follows: (select one or both of the following: "anticavity" or "fluoride") (select one of the following as appropriate: "dentifrice," "toothpaste," "treatment rinse," "treatment gel," "treatment rinse concentrated solution," "treatment rinse powder," or "treatment rinse effervescent tablets").

27. Several comments pointed out that the Panel's recommended indication for anticaries drug products in § 355.50(b), "Aids in the prevention of dental caries (decay or cavities)," is confusing and unduly restrictive with its parenthetical qualifier. The comments recommended three separate, allowable statements of indications to recognize the three ways of referring to dental caries, i.e., "Aids in the prevention of dental caries," "Aids in the prevention of dental decay," and "Aids in the prevention of dental cavities."

The agency agrees with the comments' recommendation to provide alternative terminology to recognize the different ways of referring to dental caries. The agency believes that "cavities" and "decay" are the terms that are better understood by consumers, whereas "caries" is a scientific term requiring further explanation and should be followed by the word "cavities" or "decay" in parentheses. Therefore, the agency is proposing in this tentative final monograph that the required indication read as follows: "Aids in the prevention of dental" (select one of the following: "cavities," "decay," "caries (decay)," or "caries (cavities)").

28. One comment stated that fluoride dental gels closely resemble fluoride dentifrices in terms of consistency of the products, method of application, and type of containers used. Because of these similarities, the comment suggested that dental gels should carry the same directions as dentifrices with regard to use by children 2 years of age and older. The comment recommended the following directions for dental gels: "Adults and children 2 years of age and older, children under 6 years of age should be supervised in the use of this product. Place (product name) on a clean toothbrush; brush gel over teeth surfaces. Push the slurry around the mouth and spit out excess. Do not swallow. Do not eat or drink for 30 minutes."

The Panel recommended that dental gels, i.e., fluoride gels that do not contain abrasives, not be used in children under 6 years of age because of

safety considerations. Children under 6 years of age are at a greater risk of developing adverse effects such as fluorosis (a permanent, mottled discoloration of the teeth) if excessive amounts of fluoride are repeatedly swallowed. Children under 6 years of age also have not developed control of their swallowing reflex and are not able to hold the fluoride preparation in their mouth and then expectorate properly. The Panel concluded that although children in this age group may inadvertently swallow dentifrice while brushing, the amount swallowed per average brushing is well below a toxic range. In addition, there is a lack of documentation that dental fluorosis has increased significantly following widespread use of fluoride dentifrices for approximately 20 years (45 FR 20673). (See comment 23 above.)

Dental gels are intended to be used in addition to, rather than as a substitute for, dentifrices. An excessive amount of fluoride may be ingested by a child under 6 years of age who may not have the ability to expectorate properly and who uses two fluoride products (i.e., dentifrice and gel) in addition to consuming fluoride from other sources such as fluoridated water, food, or fluoride supplements. The Panel was concerned that children under 6 years of age not be exposed to excessive fluoride; therefore, it recommended that gels and rinses be used only in children 6 years of age and older. The agency agrees with the Panel's reasoning; therefore, the Panel's recommended directions for fluoride gels are being proposed in this tentative final monograph as requested by the comment.

29. One comment requested deletion of the Panel's recommended age-restriction statements in the directions for dentifrices in § 355.50(d)(1) as follows: "adults and children 2 years of age and older" and "children under 6 years of age should be supervised in the use of this product." The comment stated that restriction of dentifrices to adults and children 2 years of age and older is unnecessary from a safety consideration and is inconsistent with the recommendation of the ADA that children be instructed in toothbrushing as early as possible and be allowed to use any approved dentifrices as soon as they are competent to do so. The comment added that references cited by the Panel at 45 FR 20673 establish that the ingestion of dentifrices by children is slight enough to justify the unsupervised use of fluoride dentifrices by all children who have been properly instructed in the use of a dentifrice.

The agency concurs that children should be instructed in brushing their teeth at an early age. However, many children 2 years of age and certainly children under 2 years of age cannot reasonably be expected to have the manual dexterity to brush properly, nor the mouthrinsing skills to expectorate properly. In a study by Ericsson and Forsman (Ref. 1) reviewed by the Panel, it was found that most 2-year-old children and some 3-year-old children could not perform mouthrinsing with water, but instead quickly swallowed the fluid. Children under 2 years of age would be more likely to swallow the dentifrice and thus increase their chance of developing dental fluorosis, a condition that can develop in children under 6 years of age who repeatedly swallow excessive amounts of fluoride.

The agency does not agree with the comment that children under 6 years of age need not be supervised in the use of a dentifrice once properly instructed in its use. The agency interprets the Panel's statement to mean that all children under 6 years of age should be properly instructed and supervised in the use of a dentifrice, but the amount of supervision may vary, depending on a child's skills. If a child has fairly good toothbrushing skills, parents may allow unsupervised brushing, but may wish to check the child's toothbrushing techniques periodically.

The age-restriction statements recommended by the Panel in § 355.50(d)(1) are not intended to discourage the use of dentifrices by children, but are intended to help parents and children use these products safely and effectively. Therefore, the Panel's age restriction recommendations are being proposed in this tentative final monograph.

Reference

(1) Ericsson, Y., and B. Forsman, "Fluoride Retained from Mouthrinses and Dentifrices in Preschool Children," *Caries Research*, 6:237–243, 1972.

30. One comment stated that it would be logical to classify fluoride dentifrices and fluoride brush-on gels in the same category with regard to label copy, warnings, restrictions, and total fluoride content per container based on a comparison of the similarities and differences between these products as shown in the following chart:

	Fluoride dentifrices	Fluoride gels
Consistency	Paste or gel	Gel.
Application	Brush on	Brush on.
Control of amount used.	Amount on brush	Amount on brush.
Container	Squeeze tube with small orifice.	Squeeze bottle with small orifice.
Container closure	Screw cap	Child proof.
Abrasives	Yes	No.

The agency acknowledges the similarities described by the comment, but concludes that fluoride dentifrices and fluoride dental gels differ in too many important respects, notably their formulations, intended uses, and methods of use, to permit the same labeling and fluoride content per container. An abrasive-containing fluoride dentifrice is intended for use in cleaning the teeth as well as aiding in the prevention of dental cavities; a nonabrasive fluoride dental gel is intended only to aid in the prevention of dental cavities and is applied after the teeth have been cleaned with an abrasive-containing dentifrice. A fluoride dental gel, to be effective, must remain on the teeth for 1 minute and then be expectorated, and the user should not eat or drink for 30 minutes after using. These time requirements do not apply to the effective use of a fluoride dentifrice. Children under 6 years of age should not use a fluoride dental gel; however, children from 2 to under 6 years of age may use a fluoride dentifrice with supervision. A fluoride dentifrice may be used more than once a day, whereas a fluoride dental gel is used only once a day. With regard to total fluorine content per container, dentifrices may contain no more than 260 mg of fluorine; dental gels are restricted to no more than 120 mg of fluorine. (See comment 4 above.)

31. Several comments recommended that § 355.50(f), which contains the ADA's product approval statement for anticaries dentifrice products, "(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," be expanded to allow the use of this labeling for dosage forms other than dentifrices (e.g., dental rinses and gels) that may be approved by ADA in the future as decay-preventive products. One comment requested that the ADA Council's Seal of Acceptance also be permitted on the label because the public recognizes the significance of the Seal used in conjunction with the statement.

The agency agrees that the labeling of dentifrices and anticaries product dosage forms other than dentifrices may include, where the product has been approved by the ADA, the ADA's

product approval statement and seal. However, under the proposed policy regarding the exclusivity of labeling terms (see comment 2 above), the agency will not include a section entitled "other allowable statements" (under which the ADA's statement was included in the Panel's recommended monograph) in final monographs for OTC drug products. As with other statements differing from the wording in the monograph, the ADA's approval statement and seal may appear on product labeling subject to the prohibitions in 21 U.S.C. 352(a) against false or misleading labeling. Therefore, § 355.50(f) is not being proposed in this tentative final monograph.

32. One comment contended that the Panel's recommendation that labeling should state the principal intended action of the active ingredient as well as the indication for use of the product (45 FR 20674) is redundant for anticaries drugs because the indication statement serves the same purpose.

The Panel's use of the term "principal intended action" is consistent with the labeling requirements for OTC drugs in 21 CFR 201.61(b), which provides that the statement of identity shall employ terms descriptive of general pharmacological categories or principal intended actions; for example, "antacid," "analgesic," "decongestant," "antihistamine", etc. The agency does not believe that the proposed statement of identity in § 355.50(a) (select one or both of the following: "anticavity" or "fluoride") (select one of the following as appropriate: "dentifrice," "toothpaste," "treatment rinse," "treatment gel," "treatment rinse concentrated solution," "treatment rinse powder," or "treatment rinse effervescent tablets,") is redundant of the agency's proposed indication statement in § 355.50(b)(1) "Aids in the prevention of dental" (select one of the following: "cavities," "decay," "caries (decay)," or "caries (cavities)")." Thus, the agency is proposing that both the statement of identity and the indication statement be included in the labeling of anticaries drug products.

33. One comment disagreed with the Panel's recommendation that the labels of OTC anticaries drug products should state the quantity of each active ingredient (45 FR 20674) because this is not required by law. The comment added that stating the quantity of each active ingredient in fluoride dentifrices may be misleading to consumers because the three principal active ingredients (sodium fluoride, stannous fluoride, and sodium monofluorophosphate) must be included in different quantities (because of their differing molecular weights) to achieve the same level of fluoride. The comment stated that a consumer who is unfamiliar with the chemical background would assume that 0.76 percent sodium monofluorophosphate, for example, provides several times the quantity of the active moiety (fluoride) provided by 0.22 percent sodium fluoride, whereas both sources provide the same quantity of fluoride.

The agency recognizes that the three active ingredients, sodium fluoride 0.22 percent, sodium monofluorophosphate 0.76 percent, and stannous fluoride 0.4 percent, are needed in different quantities to achieve the same level of fluoride in a fluoride dentifrice and that most consumers would not be familiar with these differences. The agency also recognizes that although section 502(e) of the act (21 U.S.C. 352(e)) requires disclosure of all active ingredients, there is no requirement that quantities of active ingredients in OTC drug products be listed except for specific drugs designated in the act. The three OTC anticaries active ingredients are not designated in the act. Therefore, the agency agrees with the comment that the quantities of the ingredients in fluoride toothpastes are not required in the labeling of these products.

34. One comment strongly disagreed with the Panel's conclusion that certain labeling claims are misleading and unsupported by scientific data (45 FR 20690) and contended that the labeling claim "for a healthier mouth with less decay" is clearly supported by a wealth of clinical effectiveness data. The comment also stated that the labeling claim "raising your natural resistance to tooth decay" refers to the incorporation of fluoride into dental enamel and the resulting increased resistance to acidic dissolution. The comment urged that these claims and other equivalent statements be allowed in the labeling of OTC anticaries drug products.

The agency has determined that anticaries drug products are effective in helping to prevent dental caries, thus contributing significantly to healthy teeth. Use of the term "mouth" in the comment's suggested statement "for a healthier mouth with less decay" is ambiguous. However, a statement such as "for healthier teeth with less decay" may be appropriate for anticaries drug products.

The agency has also determined that the regular use of anticaries drug products increases a person's resistance to tooth decay and believes that a statement such as "raises your resistance to tooth decay" may also be appropriate for anticaries drug products. However, the comment's suggested term "natural" would not be appropriate in this statement. The inclusion of the word "natural" may confuse consumers because the precise mechanism by which fluoride acts to reduce tooth decay remains unknown (Ref. 1). The agency believes that the statement adequately conveys the intended message to the consumer without using the term "natural."

Although the above statements may be truthful and helpful to a consumer, they do not convey a complete indication for the use of an anticaries drug product because they do not provide adequate information comparable to the required indication in § 355.50(b). Therefore, the above statements will not be included in the monograph.

However, the agency believes that the statements "for healthier teeth with less decay" and "raises your resistance to tooth decay" may be appropriate additional statements for anticaries drug products covered by this monograph and could appear in the labeling in addition to the required indication statement. As discussed in comment 2 above, the agency is proposing to amend its exclusivity rule by establishing new labeling requirements for OTC drug products. As proposed, the label and labeling of OTC drug products would be required to contain in a prominent and conspicuous location either (1) within a boxed area designated "APPROVED USES" specific wording on indications for use established under an OTC drug monograph or (2) within a nonboxed area other wording relating to such indications for use that meets the statutory prohibitions against false or misleading labeling. Thus, in either case, other wording relating to such indications for use, such as the above revised statements, would be permitted elsewhere in the labeling subject to the statutory prohibitions in 21 U.S.C. 352(a) against false or misleading labeling.

Reference

(1) Council on Dental Therapeutics, "Accepted Dental Therapeutics," 39th Ed., American Dental Association, Chicago, pp. 344–345, 1982.

35. One comment stated that the phrase "other allowable statements" that appears in § 355.50(f) of the Panel's advance notice of proposed rulemaking implies that only certain prescribed statements may be made on labels rather than a range of truthful statements and suggested that the word "allowable" be deleted from this phrase.

Under the current policy regarding the exclusivity of labeling terms (see comments 2 and 31 above), the agency will no longer include a section entitled "other allowable statements" in final monographs for OTC drug products. The agency is not proposing that such a section be included in this tentative final monograph. Therefore, it is unnecessary to further discuss the comment's request to delete the word "allowable" from the heading of this section.

36. Four comments requested deletion of the Panel's recommended labeling statement for dental rinses in § 355.50(e)(1), "This product is not a dentifrice." The comments maintained that this statement is unnecessary on dental rinses because consumers would not confuse a liquid in a bottle with a conventional dentifrice packaged in a conventional tube. One of the comments also objected to the use of the labeling statement on dental gels (see comment 25 above), but the other comments agreed with the Panel that the labeling statement is appropriate for a fluoride gel because a gel might be packaged in a conventional dentifrice tube and could conceivably be confused with a conventional dentifrice.

The agency agrees with the comments that consumers would not be apt to confuse a dental rinse with a dentifrice, but believes that a nonabrasive dental gel packaged in a conventional tube can be confused with a conventional abrasive-containing dentifrice. In addition, because fluoride dental rinses and mouthwash products (e.g., breath sweeteners) are similar in appearance, the agency is concerned that consumers may confuse these two groups of products. Proper labeling of abrasive-containing dentifrices, dental gels, and dental rinses is an important aid to preventing consumer confusion as to the use of these products. The agency is proposing to revise the statement of identity for dental gels (see comment 25 above) and is proposing to revise the statement of identity to require that dental rinses be identified as anticavity or fluoride treatment rinses to be consistent with the statement of identity for dental gels. The statements of identity for these products with the proposed revisions clearly distinguish one product from another; § 355.50(a) requires an anticaries drug product to be identified as an anticavity or fluoride dentifrice, toothpaste, anticavity or fluoride treatment rinse, anticavity or fluoride treatment gel, anticavity or fluoride treatment rinse concentrated solution, anticavity or fluoride treatment rinse powder, and anticavity or fluoride treatment rinse effervescent tablets as applicable (see comments 19 and 26 above). In order to help consumers further in distinguishing between dental gels and rinses, dentifrices, and mouthwashes, the agency proposes to revise the Panel's recommended labeling statements for dental gels and rinses in § 355.50(e) to read:

(1) *For all treatment gels.* "This is a(n)" (select one or both of the following: "anticavity" or "fluoride") "treatment gel, not a toothpaste. Read directions carefully before using."

(2) *For all treatment rinses.* "This is a(n)" (select one or both of the following: "anticavity" or "fluoride") "treatment rinse, not a mouthwash. Read directions carefully before using."

To clarify the proper use of dental rinses, the agency is proposing to revise the Panel's recommended directions in § 355.50(d)(2) to read: Adults and children 6 years of age and older: use (once or twice as appropriate) a day after brushing your teeth with a toothpaste. Vigorously swish 10 milliliters of rinse between your teeth for 1 minute and then spit out. Do not swallow the rinse. Do not eat or drink for 30 minutes after rinsing. Children under 12 years of age should be supervised in the use of this product. Children under 6 years of age: consult a dentist or doctor. The agency also proposes to revise the directions for gels under § 355.50(d)(4) to read: Adults and children 6 years of age and older: use once a day after brushing your teeth with a toothpaste. Apply the gel to your teeth and brush thoroughly. Allow the gel to remain on your teeth for 1 minute and then spit out. Do not swallow the gel. Do not eat or drink for 30 minutes after brushing. Children under 12 years of age should be supervised in the use of this product. Children under 6 years of age: consult a dentist or doctor.

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

A. Summary of Ingredient Categories

The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and has made the following changes in the categorization of anticaries active ingredients proposed by the Panel. For the convenience of the reader, the following table is included as a summary of the categorization of anticaries active ingredients recommended by the Panel and proposed by the agency.

Anticaries active ingredients	Panel	FDA
Hydrogen fluoride:		
Rinse—In an appropriate formulation with 0.02 percent fluoride ion.	NC [1]	III
Phosphate preparations:		
Calcium sucrose phosphate	II	NC [1]
Dicalcium phosphate dihydrate	II	NC [1]
Disodium hydrogen phosphate	II	NC [1]
Phosphoric acid	II	NC [1]
Sodium dihydrogen phosphate	II	NC [1]
Sodium dihydrogen phosphate monohydrate.	II	NC [1]
Sodium phosphate		
Sodium phosphate, dibasic anhydrous reagent.	II	NC [1]
Sodium bicarbonate	II	II
Sodium fluoride:		
Dentifrice—0.22 percent	I	I
Rinse—0.05 percent	I	I
Rinse—0.02 percent	NC [1]	I
Rinse—Acidulated phosphate fluoride with 0.02 percent fluoride ion.	I	I
Rinse—Acidulated phosphate fluoride with 0.01 percent fluoride ion.	NC [1]	I
Sodium fluoride and hydrogen fluoride:		
Rinse—Acidulated phosphate fluoride with 1.23 percent fluoride ion.	NC [1]	II
Sodium monofluorophosphate:		
Dentifrice—0.76 percent	I	I
Rinse—6.0 percent	II	II
Stannous fluoride:		
Dentifrice—0.4 percent	I	I
Rinse—0.1 percent	I	I
Gel—0.4 percent in an anhydrous glycerin gel.	I	I

[1] Not classified.

B. Summary of the Agency's Changes

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

1. The agency is proposing to change the term "anticaries agent" in § 355.3(b) to "anticaries drug" and to modify the definition to read as follows: "A drug that aids in the prevention of dental cavities (decay, caries)," to be consistent with the indication for anticaries drug products and the statement of identity in § 355.50(a) and to be consistent with the format of other tentative final monographs. (See comments 26 and 27 above.) In addition, the agency is proposing to change the terms "dental gel" and "dental rinse" to read either "treatment gel" and "treatment rinse" respectively in order to be consistent with the statement of identity regarding all the pertinent headings for these drug products in this tentative final monograph. (See comments 25 and 26.) The definitions regarding "dental gel" and "dental rinse" are changed accordingly. As a result of the change in these two terms, the agency is proposing to add definitions for treatment rinse concentrated solution, treatment rinse effervescent tablets, and treatment rinse

powder to the monograph as §§ 353.3(i), 353.3(j), and 353.3(k) respectively.

2. The agency is revising the introductory sentence of § 355.10 that lists anticaries active ingredients to correct a typographical error in the advance notice of proposed rulemaking and to conform to the format of other tentative final monographs. (See comment 6 above.)

3. Based on the comment stating that the Panel's classification of hydrogen fluoride as an inactive ingredient is misleading, the agency is proposing to include hydrogen fluoride in Category III as an anticaries agent. (See comment 17 above.)

4. The agency is proposing to include 0.01 percent acidulated phosphate and neutral fluoride ion treatment rinses as Category I anticaries drug products and to revise the wording in § 355.10(b)(1) by adding "the aqueous solution of" at the beginning of the statement regarding acidulated phosphate fluoride. The agency is also proposing to include directions for use of the 0.01-percent acidulated phosphate fluoride ion and a neutral fluoride ion in § 355.50(d)(2)(ii). (See comment 21 above.)

5. The agency proposes to clarify § 355.10(b) (3) and (4) by adding the phrase "with a pH of approximately 7." A freshly prepared saturated aqueous solution of sodium fluoride is described in "Merck Index" (Ref. 1) as having a pH of 7.4 and in "United States Pharmacopia XXI—National Formulary XVI," (Ref. 2) as having a pH below 7.5. "Accepted Dental Therapeutics" (Ref. 3) contains a list of acceptable 0.05 percent sodium fluoride dental rinses, two of which have a pH of approximately 7.0 with preservatives and flavoring agents. The Panel's discussion of an aqueous solution of 0.05 percent sodium gives a description of the solution as "approximately pH 7" (45 FR 20686). The agency believes that the phrase "with a pH of approximately 7" more accurately describes these dental rinses.

References

(1) Windholz, M., editor, "The Merck Index," 10th Ed., Merck and Co., Rahway, NJ, p. 1235, 1983.

(2) United States Pharmacopeia XXI—"National Formulary XVI," United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 969–970, 1985.

(3) Council on Dental Therapeutics, "Accepted Dental Therapeutics," 39th Ed., American Dental Association, Chicago, p. 353 1982.

6. The agency is proposing to include concentrated treatment rinses in the monograph. The agency is also proposing to include a warning for concentrated treatment rinses stating that these rinses should not be used before mixing with water. (See comment 19 above.)

7. The agency is proposing to revise the wording in § 355.20 concerning the package size limitations to indicate clearly that the limitations of total fluorine are per package for dentifrice, treatment rinse, and treatment gel drug products.

8. The agency is redesignating Subpart D as Subpart C and placing the labeling sections of the monograph in Subpart C.

9. The Panel's recommended statement of identity in § 355.50(a) has been expanded to include the terms "fluoride" and "toothpaste" in the labeling of anticaries drug products. (See comment 28 above.) The agency is also proposing to change the statement of identity for "dental rinse" and "dental gel" to "treatment rinse" and "treatment gel" respectively. (See comments 25 and 26).

10. The agency is proposing to change the term "caries" in § 355.50(b) in the advance notice of proposed rulemaking to allow alternative terminology for the statement of indications. The terms "cavities" and "decay" are better understood by consumers, whereas "caries" is the scientific term requiring further explanation. Therefore, the agency is proposing that the required indication for anticaries drug products read as follows: "Aids in the prevention of dental" (select one of the following: "cavities," "decay," "caries (decay)," or "caries (cavities)"). (See comment 27 above.)

11. The agency is not proposing to include the warning recommended by the Panel for treatment rinses and treatment gels in § 355.50(c): "Do not swallow. Developing teeth of children under 6 years of age may become permanently discolored if excessive amounts of flourine are repeatedly swallowed." The Panel's warning is not needed because fluoride treatment rinses and gels are not recommended for use in children under 6 years of age. However, the statement "Do not swallow the" ("rinse" or "gel" as applicable) is being included in the directions for use of these products. (See comments 22, 23, and 36 above.)

12. The agency is proposing to revise the Panel's recommended directions in § 355.50(d) (2) and (4) to include instructions to use treatment rinse or gel after cleaning the teeth with a toothpaste but not to swallow the rinse or gel, to supervise the use of rinses and gels by children under 12, and not to use rinses and gels in children under 6 years of age unless such use is approved by a dentist or doctor. (See comment 36 above.) The agency is also proposing to include directions for use in 0.01 percent fluoride ion in an acidulated phosphate and 0.01 percent fluoride ion in a neutral solution (pH of approximately 7) derived from sodium fluoride in § 355.50(d)(2)(ii). (See comment No. 21.)

13. The Panel recommended additional labeling statements for treatment gels and rinses in § 355.50(e). The agency is proposing to revise and expand the labeling in this section to aid the consumer in clearly distinguishing between abrasive containing dentifrices and nonabrasive fluoride dental gels, and between fluoride dental rinses and mouthwash products. (See comment 36 above.) The agency is redesignating the existing § 355.50(e)(2) in the Panel's recommended monograph as § 355.50(e)(3).

14. The Panel recommended additional labeling statements concerning nonpermanent staining of the teeth for stannous fluoride treatment rinses and gels. The agency is proposing to include these statements for stannous fluoride dentifrices also. (See comment 24 above.)

15. The agency is proposing to delete the section "Other allowable statements," previously designated as § 355.50(f), from the monograph. (See comments 2, 31, and 35 above.)

16. The agency is proposing to add a section, "Optional additional labeling statement," to the monograph as § 355.50(f) to allow a statement concerning the additive effect of using fluoride treatment rinses and gels to daily brushing with a fluoride dentifrice. (See comment 13 above.)

17. The agency is proposing to add a professional labeling section in the monograph to include directions for using Category I fluoride treatment rinses as fluoride supplements for ingestion. (See comment 14 above.)

18. In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs to substitute the word "doctor" for "physician" in OTC drug monographs on the basis that the word "doctor" is more commonly used and better understood by consumers. Based on comments received to these proposals, the agency has determined that final monographs and other applicable OTC drug regulations will give manufacturers the option of using either the word "physician" or the word "doctor." This tentative final monograph proposes that option.

The agency proposes to revoke the existing warning and caution statement required by § 369.21 and exemptions for certain drugs limited by NDAs to prescription sale in § 310.201(a) (10) and

(15) for anticaries drug products at the time this monograph becomes effective.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule for OTC anticaries drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act, Pub. L. 96–354. That assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC anticaries drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

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

The agency has carefully considered the potential environmental effects of the proposal and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday. FDA's regulations implementing the National Environmental Policy Act (21 CFR Part 25) have been replaced by a rule published in the **Federal Register** of April 26, 1985 (50 FR 16636, effective July 25, 1985). Under the new rule, an action of this type would require an environmental assessment under 21 CFR 25.31a(a).

Interested persons may, on or before November 29, 1985, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before January 28, 1986. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register**.

Interested persons, on or before September 30, 1986, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before December 1, 1986. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA–305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on December 1, 1986. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register**, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

List of Subjects in 21 CFR Part 355

OTC drugs; Anticaries drug products.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended by adding new Part 355, as follows:

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

Subpart A—General Provisions

Sec.
355.1 Scope.
355.3 Definitions.

Subpart B—Active Ingredients

355.10 Anticaries active ingredients.
355.20 Package size limitations.

Subpart C—Labeling

355.50 Labeling of anticaries drug products.
335.60 Professional labeling.

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

Subpart A—General Provisions

§ 355.1 Scope.

(a) 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 condition in this part and each general condition established in § 330.1.

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

§ 355.3 Definitions.

As used in this part:

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

(b) *Anticaries drug.* A drug that aids in the prevention of dental cavities (decay, caries).

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

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

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

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

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

(h) *Treatment rinse.* A liquid dosage form for delivering an anticaries drug to the teeth.

(i) *Treatment rinse concentrated solution.* A fluoride treatment rinse in a concentrated form to be mixed with water before using to result in the appropriate fluoride concentration specified in the monograph.

(j) *Treatment rinse effervescent tablets.* A fluoride treatment rinse prepared by adding an effervescent tablet (a concentrated solid dosage form) to water before using to result in the appropriate fluoride concentration specified in the monograph.

(k) *Treatment rinse powder.* A fluoride treatment rinse prepared by adding the powder (a concentrated solid dosage form) to water before using to result in the appropriate fluoride concentration specified in the monograph.

Subpart B—Active Ingredients

§ 355.10 Anticaries active ingredients.

The active ingredient of the product consists of any of the following, within the established concentration and dosage form:

(a) *Dentifrices.* (1) Sodium fluoride 0.22 percent.

(2) Sodium monofluorophosphate 0.76 percent.

(3) Stannous fluoride 0.4 percent.

(b) *Treatment rinses.* (1) An aqueous solution of 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) An aqueous solution of acidulated phosphate fluoride derived from sodium fluoride acidulated with a mixture of sodium phosphate, diabasic, and phosphoric acid to a pH of 3.5 and which yields an effective fluoride ion concentration of 0.01 percent.

(3) Sodium fluoride 0.02 percent aqueous solution with a pH of approximately 7.

(4) Sodium fluoride 0.05 percent aqueous solution with a pH of approximately 7.

(5) Sodium fluoride concentrate containing adequate directions for mixing with water before using to result in a 0.02-percent or 0.05-percent aqueous solution with a pH of approximately 7.

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

(c) *Treatment 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 drug products:

(a) *Dentifrices.* Dentifrice packages shall not contain more than 260 milligrams total fluorine per package.

(b) *Treatment rinses and treatment gels.* Treatment rinse and gel packages shall not contain more than 120 milligrams total fluorine per package.

Subpart C—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 (select one or both of the following: "anticavity" or "fluoride") (select one of the following as appropriate: "dentifrice," "toothpaste," "treatment rinse," "treatment gel," "treatment rinse, concentrated resolution," "treatment rinse powder," or "treatment rinse effervescent tablets").

(b) *Indication.* The labeling of the product states, under the heading "Indication," the following: "Aids in the prevention of dental" (select one of the following: "cavities," "decay," "caries (decay)," or "caries (cavities)")." Other truthful and nonmisleading statements, described only the indications for use that have been established and listed above, may also be used, as provided in § 330.1(c)(2) of this chapter subject to the prohibitions in section 502(a) of the act against misbranding by the use of false or misleading labeling and the prohibition in section 301(d) of the act against the introduction into interstate commerce of unapproved new drugs.

(c) *Warning.* The labeling of any concentrated treatment rinse solution, powder, or effervescent tablet contains the following warning under the heading "Warning": "Do not use before mixing with water. Read the directions carefully."

(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 doctor. Children under 6 years of age should be supervised in the use of this product.

(2) *For anticaries products marketed for use as treatment rinses*—(i) *For acidulated phosphate fluoride solution containing 0.02 percent fluoride ion, sodium fluoride 0.05 percent, sodium fluoride concentrate, and stannous fluoride concentrate identified in § 355.10(b) (1), (4), (5), and (6).* Adults and children 6 years of age and older: Use once a day after brushing your teeth with a toothpaste. Vigorously swish 10 milliliters of rinse between your teeth for 1 minute and then spit out. Do not swallow the rinse. Do not eat or drink for 30 minutes after rinsing. Children under 12 years of age should be supervised in the use of this product. Children under 6 years of age: Consult a dentist or doctor.

(ii) *For acidulated phosphate fluoride solution containing 0.01 percent fluoride ion and sodium fluoride 0.02 percent aqueous solution identified in § 355.10(b) (2) and (3).* Adults and children 6 years of age and older: Use twice a day after brushing your teeth with a toothpaste. Vigorousy swish 10 milliliters of rinse between your teeth for 1 minute and then spit out. Do not swallow the rinse. Do not eat or drink for 30 minutes after rinsing. Children under 12 years of age should be supervised in the use of this product. Children under 6 years of age: Consult a dentist or doctor.

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

(ii) *For powder or effervescent tablets used to prepare treatment rinses.* Do not use as a rinse until all the (select one of the following: "powder" or "tablet") has dissolved.

(4) *For anticaries products marketed as treament gels.* Adults and children 6 years of age and older: Use once a day after brushing your teeth with a toothpaste. Apply the gel to your teeth and brush thoroughly. Allow the gel to remain on your teeth for 1 minute and then spit out. Do not swallow the gel. Do not eat or drink for 30 minutes after brushing. Children under 12 years of age should be supervised in the use of this product. Children under 6 years of age: Consult a dentist or doctor.

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

(1) *For all treatment gels.* "This is a(n)" (select one or both of the following: "anticavity" or "fluoride") "treatment gel, not a tooth paste. Read directions carefully before using."

(2) *For all treatment rinses.* "This is a(n)" (select one or both of the following: "anticavity" or "fluoride") "treatment rinse, not a mouthwash. Read directions carefully before using."

(3) *For all stannous fluoride products intended for use as treatment rinses, treatment gels, and dentifrices.* "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) *Optional additional labeling statement.* The following labeling statement may appear in the required boxed area designated "APPROVED USES" on the label of anticaries products marketed as fluoride treatment rinses and gels. "The combined daily use of a fluoride treatment" (select one of the following: "rinse" or "gel") "and a fluoride toothpaste can aid in reducing the incidence of dental cavities."

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

§ 355.60 Professional labeling

The labeling for anticaries products marketed for use as fluoride treatment rinses identified in § 355.10(b) provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 3 to under 14 years of age: As a supplement in areas where the water supply is nonfluoridated (less than 0.3 part per million), clean the teeth with a toothpaste and rinse with 5 milliliters of 0.02 percent or 10 milliliters of 0.01 percent fluoride ion rinse daily, then swallow. When water supply contains 0.3 to 0.7 part per million fluoride ion, reduce the dose to 2.5 milliliters of 0.02 percent or 5 milliliters of 0.01 percent fluoride ion rinse daily.

Frank E. Young,

Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

Dated: August 2, 1985.

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