

DEPARTMENT OF HEALTH AND HUMAN SERVICES**Food and Drug Administration****21 CFR Parts 310, 355, and 369**

[Docket No. 80N-0042]

RIN 0910-AA01

Anticaries Drug Products for Over-the-Counter Human Use; Final Monograph**AGENCY:** Food and Drug Administration, HHS.**ACTION:** Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing conditions under which over-the-counter (OTC) anticaries drug products (products that aid in the prevention of dental cavities) are generally recognized as safe and effective and not misbranded. FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and all new data and information on OTC anticaries drug products that have come to the agency's attention. This final monograph is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: October 7, 1996.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-5000.

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 (the Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by 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, after deletion of a small amount of trade secret information, were placed on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23,

12420 Parklawn Dr., Rockville, MD 20857.

The agency's proposed regulation, in the form of a tentative final monograph, for OTC anticaries drug products was published in two segments. The first segment was published in the *Federal Register* of September 30, 1985 (50 FR 39854). It addressed general issues on OTC anticaries drug products, the switch of prescription anticaries drug products to OTC status, specific anticaries active ingredients, dosages for anticaries active ingredients, and labeling of anticaries drug products. Interested persons were invited to file by November 29, 1985, written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs (the Commissioner). Interested persons were invited to file comments on the agency's economic impact determination by January 28, 1986. New data could have been submitted until September 30, 1986, and comments on the new data until December 1, 1986.

The agency stated in the advance notice of proposed rulemaking that the Panel's recommended Laboratory Testing Profiles (LTP's) represented a new concept with many technical issues yet to be resolved. Thus, the LTP's were not included in the first segment of the tentative final monograph. The agency mentioned in the tentative final monograph (50 FR 39854) that an open public meeting was held on September 26 and 27, 1983, to discuss unresolved technical issues concerning the LTP's. The LTP's were subsequently discussed in the second segment of the tentative final monograph, published in the *Federal Register* of June 15, 1988 (53 FR 22430). This amendment of the tentative final monograph addressed final formulation testing for monograph active ingredients in dentifrice formulations and issues relating to this testing. Interested persons were invited to file by October 13, 1988, written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner. Interested persons were invited to file comments on the agency's economic impact determination by October 13, 1988. New data could have been submitted until June 15, 1989, and comments on the new data until August 15, 1989.

In a notice published in the *Federal Register* of May 8, 1992 (57 FR 19823), the agency reopened the administrative record to include data and information in support of a request to increase the package size limitation for fluoride dentifrice drug products from not more than 260 milligrams (mg) of total fluorine per package to not more than

350 mg. Interested persons were invited to submit written comments by July 7, 1992.

In the *Federal Register* of November 24, 1992 (57 FR 55199), the agency also reopened the administrative record to obtain public comment on whether the labeling of OTC fluoride-containing drug products should include the quantity of fluoride, i.e., the specific amount of fluoride present in the product. Interested persons were invited to submit written comments by January 25, 1993. In the *Federal Register* of January 26, 1993 (58 FR 6102), the agency extended the comment period to March 26, 1993.

This final rule encompasses all of the above segments. Final agency action on all OTC anticaries drug products occurs with the publication of this final rule establishing a monograph for OTC anticaries drug products.

The OTC drug procedural regulations, (§ 330.10) provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA is no longer using 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. In place of Category I, the term "monograph conditions" is used; in place of Category II or III, the term "nonmonograph conditions" is used.

As discussed in the proposed regulation for OTC anticaries drug products (50 FR 39854), the agency advised that the conditions under which the drug products that are subject to this monograph will be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication in the *Federal Register*. Therefore, on or after October 7, 1996, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application or abbreviated application (hereinafter called application). Further, any OTC drug product subject to this monograph

that is repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In response to the proposed rule, the amended proposed rule, and the two reopenings of the administrative record for OTC anticaries drug products, 19 drug manufacturers, 2 drug manufacturers associations, 2 health care professionals, 1 health care professional society, and 3 academic institutions submitted comments. Copies of the comments are on public display in the Dockets Management Branch (address above.) Additional information that has come to the agency's attention since the publication of the proposed rule, amended proposed rule, and notices to reopen the administrative record is also on display in the Dockets Management Branch.

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 Conclusions on the Comments

A. General Comments on Anticaries Drug Products

1. One comment noted its continuing position that FDA could not legally and should not, as a matter of policy, prescribe exclusive lists of terms from which indications for use for OTC drug products must be drawn. The comment stated that FDA could not legally prohibit alternative OTC indications for use in terminology that is otherwise truthful and not misleading. The comment added that its views on this subject were presented in oral and written testimony submitted to FDA in connection with the September 29, 1982, FDA hearing on the exclusivity policy. The comment noted that a proposed revision to the exclusivity policy had been published on April 22, 1985 (50 FR 15810). The comment mentioned that it had submitted its views in response to that proposal and was incorporating those views into the rulemaking for OTC anticaries drug products. A second comment strongly

supported the proposed revision of the exclusivity policy and discussed a number of constitutional and policy concerns about the agency's labeling policies for OTC drug products.

The agency notes that the comments in the current rulemaking were submitted before the agency published a final rule changing its labeling policy for stating the indications for use of OTC drug products in the *Federal Register* of May 1, 1986 (51 FR 16258). The comments' concerns were addressed by the agency's change in its labeling policy for stating indications for use. Under the new policy in § 330.1(c)(2) (21 CFR 330.1(c)(2)), the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either: (1) The specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "APPROVED USES"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "APPROVED USES"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "APPROVED USES"; plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling.

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

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products, published in the *Federal Register* of May 11, 1972 (37 FR 9464 at 9467 to 9472); in paragraph 3 of the preamble to the tentative final monograph for OTC antacid drug products, published in the *Federal Register* of November 12, 1973 (38 FR 31260); and in paragraph 1 of the preamble to the tentative final monograph in the present proceeding (50 FR 39854 at 39855). FDA reaffirms the conclusions stated in those documents. Court decisions have confirmed the agency's authority to issue substantive regulations by informal rulemaking. (See, e.g., *National Nutritional Foods Association v. Weinberger*, 512 F.2d 688, 696-698 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers v. FDA*, 487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd*, 637 F.2d 887 (2d Cir. 1981).)

3. One comment noted that interested persons must file new data within 1 year after publication of a tentative final monograph per 21 CFR 330.10(a)(7)(iii). For this reason, the comment contended that it is important that persons submitting comments or objections to the tentative final monograph be provided with early feedback from FDA so that sufficient time will remain to allow any necessary additional testing or market research. The comment requested that the agency provide feedback on requests no later than 6 months following the submission of comments or objections to the proposed rule. The comment also asked that the agency's regulations for the OTC drug review be amended to contain this provision.

The agency is unable to make a specific commitment to provide feedback on all comments and objections received in this and other OTC drug rulemakings within a specific time frame, as requested by the comment. Competing priorities and the constraints of limited resources make this impossible to do. However, the agency does review all comments and objections and tries to provide timely feedback as the situation requires and as workloads permit.

4. The Public Health Service Ad Hoc Subcommittee on Fluoride of the Committee to Coordinate Environmental Health and Related Programs (the Subcommittee) discussed dental fluorosis resulting from fluoride intake in its report entitled "Review of Fluoride: Benefits and Risks" (Ref. 1). The Subcommittee stated that dental fluorosis only occurs during tooth formation and becomes apparent upon eruption of the teeth. Dental fluorosis ranges from very mild (symmetrical whitish areas on teeth) to severe (pitting of the enamel, frequently associated with brownish discoloration). The Subcommittee recommended that manufacturers of dental products explore whether the levels of fluoride in their products can be reduced while preserving clinical effectiveness. (However, the Subcommittee did not suggest an acceptable fluoride exposure level.) In response to the Subcommittee's recommendation, the agency asked a professional dental association and two manufacturers associations (Refs. 2, 3, and 4) for information on dentifrices containing low levels of fluoride, particularly for use by children 2 to under 6 years of age.

The dental association stated that it is not currently considering a low fluoride toothpaste, but would evaluate such a product if one were to be submitted.

The association indicated that such a product would be accepted if clinical data demonstrating effectiveness were available.

The two manufacturers associations provided a joint response, in which they reviewed the report and relevant clinical and epidemiological literature, with the following conclusions: (1) There is a lack of scientific support for a cause and effect relationship between the ingestion of fluoride from dentifrice products and the subsequent development of enamel fluorosis; (2) the reported increase in enamel fluorosis, which ranges from very mild to mild, appears to be a result of factors other than dentifrice use, while, importantly, dentifrice use has been the principal contributor to the caries decline over the past 20 years; and (3) manufacturing changes to reduce the fluoride content of baby formulas, as well as cautionary advice to physicians about the administration of fluoride supplements to young children, are steps that have already been initiated and may well counteract the increase of the very mild to mild forms of enamel fluorosis that have been reported, as new epidemiologic data become available in the future.

The manufacturers associations recommended that there be no reduction in the 850- to 1,150-parts per million (ppm) theoretical total fluorine levels proposed in the tentative final monograph for OTC anticaries drug products, contending that any reduction in this range could have serious public health consequences in terms of reducing the current level of anticaries protection in young children. The associations noted that data from studies evaluating low-potency (250 to 550 ppm) fluoride dentifrices were contradictory and very sparse in children 2 to 6 years of age.

The agency agrees that there is not enough evidence available at this time to support the safety and effectiveness of a low-fluoride dentifrice for children 2 to under 6 years of age, or to determine an appropriate fluoride concentration for a low-level dentifrice. As noted by the Subcommittee, dental fluorosis does not compromise oral health or tooth function as do dental caries. Therefore, the risk of dental caries from inadequate fluoride protection is a greater health hazard than the cosmetic detriment of fluorosis. Until adequate data become available, the agency is not able to generally recognize a low-fluoride dentifrice as safe and effective. If data become available, the agency will consider them.

References

(1) Department of Health and Human Services, "Review of Fluoride Benefits and Risks: Report of the Ad Hoc Subcommittee on Fluoride, of the Committee to Coordinate Environmental Health and Related Programs," February, 1991, in OTC Vol. No. 08AFM, Docket No. 80N-0042, Dockets Management Branch.

(2) Comment No. LET15, Docket No. 80N-0042, Dockets Management Branch.

(3) Comment No. LET16, Docket No. 80N-0042, Dockets Management Branch.

(4) Comment No. LET17, Docket No. 80N-0042, Dockets Management Branch.

5. One comment stated that the proposed definitions for dentifrice, treatment gel, and treatment rinse in § 355.3(d), (g), and (h), respectively, should be revised to exclude discussion of the "cosmetic function or nonfunction" of these treatment categories. The comment noted, for example, that the first sentence in the definition for dentifrice, "A substance used with a toothbrush to clean the accessible surfaces of the teeth," refers to a cosmetic function and should be deleted. The comment proposed modifying the definitions for dentifrice and treatment gel to be consistent with the definition for a treatment rinse as follows: A dentifrice is an abrasive-containing dosage form for delivering an anticaries drug to the teeth, a treatment gel is a gel dosage form for delivering an anticaries drug to the teeth, and a treatment rinse is a liquid dosage form for delivering an anticaries drug to the teeth. The comment suggested the following alternative definition for the entire category of anticaries drug products rather than defining individual dosage forms: "an anticaries drug product is one which aids in the prevention or treatment of dental caries. It may be formulated as an abrasive-containing paste or powder, nonabrasive-containing gel, liquid rinse, or other appropriate product types." The comment concluded that this alternative definition more clearly emphasizes the intended use of these products rather than emphasizing the dosage form.

Another comment requested that some proposed definitions of OTC anticaries dosage forms be revised to delete those terms that refer to both therapeutic and cosmetic functions. The comment specifically referred to the definitions in § 355.3(a) (abrasive), (d) (dentifrice), (g) (treatment gel), (h) (treatment rinse), (i) (treatment rinse concentrated solution), (j) (treatment rinse effervescent tablets), and (k) (treatment rinse powder). The comment contended that the combination of therapeutic and cosmetic functions in these definitions would be confusing

and inappropriate. The comment recommended that this section be revised to more clearly emphasize the intended therapeutic function of these dosage forms. For example, "an anticaries drug product is one which aids in the prevention or treatment of dental caries (decay, cavities) and may be formulated as an abrasive-containing dentifrice, paste, or powder, nonabrasive gel, liquid rinse, or effervescent powder or tablets."

The agency has reviewed the Panel's evaluation of the definition of different fluoride dosage forms and concludes that there is a significant difference between dentifrices and nonabrasive dental gels and rinses. A dentifrice formulation contains an abrasive that is included in the formulation to clean the teeth (45 FR 20666 at 20671), while nonabrasive dental gels and rinses do not (45 FR 20666 at 20671).

The agency agrees with the comments that OTC drug monographs should not regulate cosmetic claims and are limited to only drug claims. The monograph definitions are intended to refer to the therapeutic uses of the dosage forms defined. Accordingly, the agency is deleting any references to a "cosmetic function" (e.g., cleaning) from the proposed definitions. In the definition for dentifrice, the first sentence ("A substance used with a toothbrush to clean the accessible surfaces of the teeth.") is deleted. The second sentence is revised to read "An abrasive-containing dosage form for delivering an anticaries drug to the teeth." In the definition for treatment gels, the words "and are not intended for use in cleaning the teeth" are deleted. Other definitions mentioned by the comment (treatment rinse, treatment rinse concentrated solution, treatment rinse effervescent tablets, and treatment rinse powder) do not need to be revised because they do not contain any "cosmetic functions" language.

6. One comment recommended that the definition of an "anticaries drug," proposed in § 355.3(b) as "a drug that aids in the prevention of dental cavities (decay, caries)," be revised to include "treatment" in addition to "prevention" of dental cavities. The comment also requested that the definition of "anticaries drug" reflect the various product dosage forms by adding the following sentence to the definition: "It may be formulated as an abrasive-containing paste or powder, nonabrasive-containing gel, liquid rinse, or other appropriate product type." The comment indicated that the expanded definition more clearly defines an anticaries drug and encompasses the various product dosage forms.

The agency does not agree that the term "treatment" alone should be added to the definition of an anticaries drug. In the context of this definition, the word "treatment" alone implies that anticaries drug products could treat an existing caries lesion rather than being useful as a preventive treatment. The Panel recommended and the agency previously proposed conditions under which OTC anticaries drug products that aid in the prevention of dental cavities would be generally recognized as safe and effective, and not misbranded (45 FR 20666 at 20690 and 50 FR 39854 at 39871). Treatment of dental cavities is generally understood to be a process by which medical or dental intervention in the management of cavities results in either repair or stabilization of tooth decay. Neither the Panel nor the agency received data indicating that fluoridated compounds included in the monograph are effective in treating or stabilizing tooth decay. The fluoride drugs included in the monograph are intended as preventive measures against tooth decay and not as treatment modalities for the management of existing dental cavities. However, if the term "treatment" is expanded to read "prophylactic treatment," the preventive nature of such "treatments" would not necessarily imply treatment of an existing caries lesion. Prophylactic treatment is generally described as the act or manner of protection for or prevention of disease. Thus, the agency is adding the term "prophylactic treatment" in the definition for "anticaries drug" in § 355.3(c) of this final monograph.

The agency does not agree with the comment that the definition of "anticaries drug" should specify various dosage forms. The definition is only included in the monograph to reflect the intended use of these drug products.

The agency agrees with the comment that an "anticaries drug" can be formulated in various dosage forms and has defined numerous dosage forms in the final monograph (see § 355.3(e) and (h) through (m)). These dosage forms include those requested by the comment.

7. Two comments objected to the second sentence of the definition for "treatment gel" in proposed § 355.3(g), which reads: "Treatment gels are formulated in an anhydrous glycerin base with suitable thickening agents included to adjust viscosity." The comments indicated that treatment gels, including 0.4-percent stannous fluoride treatment gel, may be formulated in bases that do not contain any anhydrous glycerin compound without

compromising the safety or effectiveness of the anticaries drug product. Therefore, the comments recommended that the agency delete the second sentence of the definition.

The agency does not agree that the second sentence of the definition of a "treatment gel" should be deleted. The definition in proposed § 355.3(g) was based on the only formulation for this dosage form that was submitted to the Panel for review. The Panel stated that stannous fluoride is stable in anhydrous glycerin (45 FR 20666 at 20688) and defined "dental gels" as being "formulated in an anhydrous glycerin base with suitable thickening agents included to adjust viscosity" (45 FR 20690). The Panel (45 FR 20688) and the agency have used this definition based on the results of laboratory and clinical studies that supported the safety and effectiveness of a specific formulation. For greater clarity, the agency is changing the term "treatment gel" in § 355.3(i) to "preventive treatment gel" to make it clear that the product's intended purpose is prevention of dental cavities. Preventive treatment gels formulated in bases other than anhydrous glycerin could be considered for inclusion in the monograph provided that stability of the fluoride compound is demonstrated and the available fluoride ion is not adversely affected by the base used in the formulation. If such a formulation were found acceptable, the definition of a preventive treatment gel could be revised as necessary to describe such a formulation. However, the agency currently has no data to support such formulations. Accordingly, the agency is not revising the definition at this time.

8. One comment disagreed with the agency's suggestion in the tentative final monograph (53 FR 22430 at 22432) that interested persons may petition the agency to amend the anticaries monograph to include specific organic fluorides as active ingredients for use in dental formulations rather than file to obtain an approved new drug application (NDA). The comment stated that allowing submission of a petition to include organic fluorides in the monograph presupposes that these active ingredients can be shown to be generally recognized as safe and effective, and have been used for a material time and to a material extent. The comment noted that although organic fluoride formulations have been used outside the United States, they do not meet the conditions for inclusion in the OTC drug review because they have never been sold in this country. The comment therefore suggested that the agency not allow the alternative of

petitioning to amend the monograph to include organic fluoride formulations, but instead require filing an NDA.

The agency agrees with the comment that organic fluoride formulations do not have a marketing history in the United States. However, the agency is currently reevaluating whether foreign marketing can satisfy the material time and extent criteria for inclusion of an ingredient in the OTC drug review. The agency intends to address this issue in a future issue of the *Federal Register*. In the meantime, it would not be in the public interest to unduly delay publication of the final monograph for OTC anticaries drug products while this matter is being resolved.

Interested persons may submit a petition requesting amendment of the final anticaries monograph to include an organic fluoride formulation. Such a petition would be considered in the context of the agency's reevaluation of the marketing history threshold criteria for the OTC drug review. Alternatively, an NDA may be filed under part 314 (21 CFR part 314). With either procedure, the manufacturer must submit adequate data showing the organic fluoride to be safe and effective for its intended use.

B. Comments on Specific Anticaries Active Ingredients and Dosage Forms

9. One comment requested that the agency consider the anticaries activities of both the stannous and the fluoride ions in 0.4 percent stannous fluoride, as well as the combined anticaries effect of the total compound, instead of considering the fluoride ions alone. The comment contended that the stannous ions in 0.4 percent stannous fluoride have significant anticaries properties, by reducing enamel solubility and through antibacterial activity. However, the comment did not submit any data to support its position.

The Panel reviewed extensive data on stannous fluoride dentifrices, rinses, and gels (45 FR 20666 at 20684 to 20685 and 20687 to 20688) and attributed effectiveness to the fluoride ion present in the product. The agency is not aware of any data supporting anticaries activity of stannous ions in stannous fluoride. Without data demonstrating this activity, the agency has no basis to consider the stannous ions as contributing to the anticaries effects of these drug products.

10. Several comments requested that the allowable upper limit of fluoride concentration in a dentifrice marketed under the final monograph be increased from 1,150 ppm theoretical total fluorine to 1,500 ppm. The comments stated that 850 to 1,150 ppm levels of fluoride in dentifrice products were

established nearly 25 years ago. One comment mentioned that, at that time, concentrations of fluoride were set arbitrarily low because of concerns about fluoride toxicity. The comments indicated that there is sufficient evidence that much higher fluoride concentrations are safe and effective, based on widespread use of such concentrations in the United States and Europe. With more toxicological data now available, the comments suggested a higher dosage of fluorides in dentifrices should be available for persons who reside in nonfluoridated areas or who have a greater propensity to develop caries. The comments contended that such a need has been acknowledged by the agency's approval of an NDA for an "extra-strength" (1,500 ppm) fluoride dentifrice. One comment indicated that it manufactures and distributes "extra-strength" fluoride dentifrices in other countries and has received no reports of ill effects from use of these products.

The comments submitted several clinical studies (Refs. 1, 2, and 3) demonstrating that a dentifrice containing 1,500 ppm theoretical total fluoride can provide greater anticaries protection than 850- to 1,150-ppm levels. The first study (Ref. 1) was a 3-year, double-blind clinical comparison of the anticaries effectiveness of a test dentifrice containing 1.14 percent sodium monofluorophosphate (1,500 ppm theoretical total fluoride) with a control dentifrice containing 0.76 percent sodium monofluorophosphate (1,000 ppm theoretical total fluoride). This study involved 2,415 children, primarily 8 to 11 years of age, who resided in a nonfluoridated community. The children were randomly assigned to one of the two groups. The children brushed normally at home and participated in a daily supervised toothbrushing exercise at school. Results of this study indicated that 48 percent of the subjects who used the 1,000-ppm fluoride dentifrice remained caries free and 57 percent of those who used the 1,500-ppm dentifrice remained caries free. The study also suggested that the participants using the 1,000-ppm dentifrice would have projected a savings of 639 additional surfaces and 344 teeth if they had received the 1,500-ppm dentifrice during the 3-year trial.

The second study (Ref. 2) was also a 3-year, double-blind clinical comparison of two sodium monofluorophosphate dentifrices, one containing 1,500 ppm and the other containing 1,000 ppm theoretical total fluoride. The study involved 1,913 children between 6 and 11 years of age. The subjects were randomly assigned to

one of the two groups. The children brushed in the same manner as in the first study. Results of this study demonstrated that, even in an area with optimal water fluoridation, a 1,500-ppm concentration provides greater anticaries protection than a 1,000-ppm theoretical total fluoride concentration.

The third clinical study (Ref. 3) compared the anticaries effect of three dentifrices containing the following concentrations of theoretical total fluoride: (1) 1,100 ppm (as sodium fluoride), (2) 2,800 ppm (as sodium fluoride), and (3) 2,800 ppm (as sodium monofluorophosphate). Approximately 4,500 school children between 7 and 15 years of age, whose community water supply contained less than 0.3 ppm fluoride, were assigned at random to brush unsupervised with one of the three dentifrices. Results of the 3-year clinical study showed no significant difference between the 2,800-ppm sodium monofluorophosphate and the positive control (1,100 ppm as sodium fluoride). However, the study demonstrated that the group assigned to brush with sodium fluoride containing 2,800 ppm theoretical total fluoride received an estimated 15 percent fewer cavities than those subjects who brushed with the sodium fluoride dentifrice containing 1,100 ppm theoretical total fluoride.

One comment noted that two of these clinical studies (Refs. 1 and 2) formed the basis for FDA approval of the 1,500-ppm "extra-strength" dentifrice under an NDA. Based on these data, the comment requested that the 1,500-ppm dentifrice be included in the monograph.

One comment requested that the agency specifically include higher strength sodium fluoride dentifrice products (1,500 ppm) in the final monograph. The comment stated its belief that consumers should be permitted the widest possible choice of safe and effective OTC drugs and that the monograph should be flexible to permit the use of equivalent fluoride species.

Several other comments argued that increasing the fluoride concentration to a level as high as 1,500 to 1,650 ppm would be unwise without adequate scientific support to justify the increased risk of developing fluorosis. One comment indicated that clinical trials using higher strength fluoride-containing dentifrices have demonstrated no adverse experiences or changes of any consequence with respect to soft tissue aberrations in children 8 to 12 years of age. However, the comment added that there has not been sufficient attention paid to the

potential risk of enamel fluorosis in children under 6 years of age using such higher strength fluoride dentifrices, particularly if the children live in an optimally-fluoridated community. Another comment cited two reports (Refs. 4 and 5) indicating that the prevalence of dental fluorosis in children residing in nonfluoridated areas has increased appreciably during the past decade with more than 20 percent of the children having mild fluorosis. The comment also cited another study (Ref. 6) suggesting that the use of fluoride dentifrices prior to 2 years of age is a major risk factor for dental fluorosis. The comment pointed out that modifying the monograph to permit the use of elevated fluoride concentrations in dentifrices (i.e., 1,500 to 1,650 ppm) would clearly increase the risk of children developing dental fluorosis. The comment further stated that the modest increase in anticaries effectiveness attributable to elevated fluoride levels in dentifrices may not be adequate to justify the increased risk of developing fluorosis. The comment concluded that the proposed increase of fluoride in dentifrices to 1,500 ppm would affect the risk/benefit ratio unfavorably. Accordingly, the comment urged the agency to reject the proposed increase in the fluoride level in dentifrices to 1,500 to 1,650 ppm.

Another comment expressed similar concern for the potential risk of enamel fluorosis in children under 6 years of age who may use dentifrices containing the proposed higher levels of fluoride during toothbrushing. The comment indicated that there exists ample documentation that young children swallow a significant amount of dentifrice. The comment submitted two published clinical studies (Refs. 7 and 8) evaluating the significance of fluoride dentifrices as a risk factor in dental fluorosis. One study (Ref. 7) indicated that a portion of the dentifrice introduced to the mouth and not expectorated, but swallowed and absorbed, ranged from 0 to 100 percent. The study suggested that inadequate control of the swallowing reflex by younger children accounts for the excessive ingestion of fluorides, particularly from dentifrices and mouthrinses. The other study (Ref. 8) indicated that, on average, children used 0.662 gram (g) of dentifrice and ingested 0.299 g per brushing. Results from this study indicated: (1) The younger the children, the more likely they are to swallow a greater proportion of dentifrice; and (2) young children who rinse their mouths and expectorate properly after brushing ingest less

dentifrice. The comment predicted that if manufacturers are allowed to market an increased level of fluoride without requiring an agency-approved application, routine use of these extra strength dentifrices would increase the potential risk of enamel fluorosis in younger children. However, the comment did not indicate how or why the routine use of NDA-approved extra strength dentifrice products would prevent an increased risk of enamel fluorosis in younger children.

In the tentative final monograph for OTC anticaries drug products (53 FR 22430 at 22432), the agency stated that a 1,500-ppm theoretical total fluoride level is safe, but indicated that general recognition of the effectiveness of this strength fluoride dentifrice must be based on adequate published or publicly available medical and scientific data. Two clinical studies (Refs. 1 and 2) that formed the basis of an agency NDA approval of this strength sodium monofluorophosphate dentifrice have now been included in the public record for this rulemaking by the NDA holder. Results of these studies indicate an enhanced anticaries benefit derived over a 3-year period from the use of the higher fluoride sodium monofluorophosphate dentifrice (1,500 ppm) when compared to the positive control fluoride dentifrice (1,000 ppm). The studies also indicated that children who are at increased risk to develop caries and those with erupting premolars and second molars may derive more benefit from a 1,500-ppm dentifrice than a 1,000-ppm dentifrice.

The agency has not received any clinical or available fluoride ion data on any 1,500-ppm sodium fluoride dentifrice comparable to the information for 1,500-ppm sodium monofluorophosphate dentifrice. Therefore, the agency is not including higher strength (1,500 ppm) sodium fluoride dentifrice drug products in this final monograph at this time.

As noted above, comments expressed concern that an increase of theoretical total fluoride to 1,500 ppm could increase the incidence of dental fluorosis in children. The agency agrees that for children under 6 years of age a risk/benefit analysis indicates that levels of fluoride in dentifrices should not exceed the currently accepted OTC level of 1,150 ppm (see discussion of fluorosis in comment 23). Although an NDA was approved in 1986 for an extra-strength fluoride dentifrice (1,500 ppm) whose labeling allowed for use in children above 2 years of age, the agency recognizes that more recent data (Refs. 4 and 8) suggest that the incidence of fluorosis in children under

6 years of age is increasing in the United States. The agency does not believe that the increased risk of fluorosis outweighs the benefit of using an extra-strength fluoride dentifrice in children under 6 years of age. The agency has determined from the results of the submitted clinical studies that the enhanced benefit of using an extra-strength dentifrice product does not present additional risk to children above 6 years of age and to adults, particularly for those with a greater propensity to develop cavities or for those who live in communities with nonfluoridated water. As discussed in the tentative final monograph (50 FR 39854 at 39864), developing teeth of children under 6 years of age may show objectionable dental fluorosis from repeated ingestion of excessive amounts of fluoride. However, 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 the amount and frequency of use of fluoride dentifrices.

The agency is including sodium monofluorophosphate dentifrices that contain 1,500 ppm theoretical total fluoride in this final monograph. Because of concerns about dental fluorosis, the agency is requiring that dentifrice products with these fluoride concentrations be clearly labeled for use only by children above 6 years of age. Accordingly, the agency is including the following directions in § 355.50(d)(1)(ii):

Paste dosage form with a theoretical total fluoride concentration of 1,500 ppm identified in § 355.10(b)(2). Adults and children 6 years of age and older: brush teeth thoroughly, preferably after each meal or at least twice a day, or as directed by a dentist or doctor. Instruct children under 12 years of age in good brushing and rinsing habits (to minimize swallowing). Supervise children as necessary until capable of using without supervision. Children under 6 years of age: Do not use unless directed by a dentist or doctor.

The agency believes that extra-strength fluoride dentifrice products may be beneficial to consumers who have a greater propensity to develop cavities, and that manufacturers may wish to promote these products for this purpose. Therefore, the agency is expanding § 355.50(f)(2) to include an optional additional labeling statement for these products as follows:

For dentifrice products containing 1,500 ppm theoretical total fluoride. Adults and children over 6 years of age may wish to use this extra-strength fluoride dentifrice if they reside in a nonfluoridated area or if they have a greater tendency to develop cavities.

Finally, the agency does not find that sufficient data exist to support the safety and effectiveness of a theoretical total

fluorine level above 1,500 ppm. Accordingly, the agency is not including dentifrices with such theoretical total fluoride levels in the monograph.

References

- (1) Conti, J. A. et al., "A 3-year Clinical Trial to Compare Efficacy of Dentifrices Containing 1.14 Percent and 0.76 Percent Sodium Monofluorophosphate," *Community Dental Oral Epidemiology*, 16:135-138, 1988.
 - (2) Fogels, H. R. et al., "A Clinical Investigation of a High-Level Fluoride Dentifrice," *Journal of Dentistry for Children*, 55(3):210-215, 1988.
 - (3) Lu, K. H. et al., "A Three-year Clinical Comparison of a Sodium Monofluorophosphate Dentifrice with Sodium Fluoride Dentifrices on Dental Caries in Children," *Journal of Dentistry for Children*, 54(4):241-244, 1987.
 - (4) Woolfolk, M. W. et al., "Relation of Sources of Systemic Fluoride to Prevalence of Dental Fluorosis," *Journal of Public Health Dentistry*, 49:78-82, 1989.
 - (5) Leverett, D. H., "Fluorides and the Changing Prevalence of Dental Caries," *Science*, 217:26-30, 1982.
 - (6) Osuji, O. O. et al., "Risk Factors for Dental Fluorosis in a Fluoridated Community," *Journal of Dental Research*, 67(12):1488-1492, 1988.
 - (7) Whitford, G. M., D. W. Allmann, and A. R. Shahed, "Topical Fluorides: Effects on Physiologic and Biochemical Processes," *Journal of Dental Research*, 66(5):1072-1078, 1987.
 - (8) Simard, P. L. et al., "The Ingestion of Fluoride Dentifrice by Young Children," *Journal of Dentistry for Children*, 56:177-181, 1989.
11. One comment (from the holder of the only approved NDA for a 1,500-ppm fluoride dentifrice) provided data indicating that the lowest available fluoride ion concentration measured during the 3-year clinical trial of its 1,500-ppm sodium monofluorophosphate dentifrice product was 1,295 ppm, with an analytical variability of ± 20 ppm (Refs. 1 and 2).

Based on the available fluoride ion data for this product, the agency has determined at this time that all 1,500-ppm sodium monofluorophosphate dentifrices must provide an available fluoride ion concentration equal to or greater than 1,275 ppm. Accordingly, the agency is including higher strength (1,500 ppm) sodium monofluorophosphate dentifrice products in § 355.10(b)(2) of this final monograph as follows:

Dentifrices containing 1,500 ppm theoretical total fluoride in a paste dosage form. Sodium monofluorophosphate 1.153 percent with an available fluoride ion concentration (consisting of PO_3F^- and F^- combined) $\approx 1,275$ ppm.

References

(1) Comment LET18, Docket No. 80N-0042, Dockets Management Branch.

(2) Comment LET20, Docket No. 80N-0042, Dockets Management Branch.

12. One comment requested that the active ingredient listings for sodium fluoride treatment rinses in proposed § 355.10(b)(3), (b)(4), and (b)(5) be combined as follows: "Sodium fluoride 0.02 to 0.05 percent in a final solution with a pH of approximately 7." The comment stated that this would provide a range of allowable concentrations for these rinses without affecting the technical accuracy of the monograph.

The agency disagrees with the comment. The active ingredient listings in § 355.10(b)(3), (b)(4), and (b)(5) specify particular concentrations for sodium fluoride in a rinse dosage form. The monograph is not intended to provide a range of concentrations for these products. The 0.02- and 0.05-percent sodium fluoride concentrations were included in the monograph based on separate, independent clinical studies, as discussed for the 0.05-percent concentration in the Panel's report (45 FR 20666 at 20686) and for the 0.02-percent concentration in the agency's tentative final monograph (50 FR 39854 at 39863). More importantly, the directions for 0.02 percent sodium fluoride in a neutral dental rinse (pH of approximately 7) are for use twice daily and for 0.05 percent sodium fluoride rinse are for use only once a day. These dosage regimens are each supported by separate, independent clinical data. There are no data to support directions for other concentrations. Accordingly, there is no basis to combine the active ingredient listings for the sodium fluoride treatment rinses included in this final monograph.

13. One comment requested that sodium fluoride/sodium bicarbonate powdered dentifrices be included in the final monograph for OTC anticaries drug products. In response to the agency's concerns discussed in the tentative final monograph (53 FR 22430 at 22443) about the safety and effectiveness of powdered fluoride dentifrices, the comment submitted several analytical and biological studies (Ref. 1). The comment contended that these studies demonstrate the effectiveness and comparable bioavailability of a powdered fluoride dentifrice with a toothpaste containing a similar abrasive system and an equivalent concentration of theoretical total fluorine.

The comment submitted several animal studies (Refs. 2, 3, and 4) that determined the anticaries effect of a sodium fluoride/sodium bicarbonate powdered dentifrice in rats that were

infected with highly virulent strains of cariogenic bacteria. In one study (Ref. 2), a group of rats infected with *Streptococcus sobrinus* that was treated topically with sodium fluoride/sodium bicarbonate powdered dentifrice experienced 42 percent fewer caries lesions than a control group treated only with distilled water. Rats exposed to either the tooth powder or 10 ppm fluoridated drinking water produced similar reduction in caries (42 and 47 percent, respectively).

In another study (Ref. 3), rats infected with *S. mutans* were treated with a 1:2 part slurry of sodium bicarbonate-based powdered dentifrice containing 0.22 percent sodium fluoride (1,000 ppm) in water for 1 minute daily for 3 weeks. Results indicated a 51-percent caries reduction in infected rats treated with the tooth powder as compared to the group of rats treated with distilled water. Rats treated with an equal concentration of sodium fluoride aqueous solution without other inactive ingredients developed a 36-percent reduction in cavities as compared to the control group. The data also indicated that no significant difference in the incidence of cavities was observed in the group of rats treated topically with sodium fluoride/sodium bicarbonate powdered dentifrice and the group of rats receiving no other treatment except 10 ppm fluoride in their drinking water (51 percent versus 54 percent).

In another animal study (Ref. 4), rats infected with *S. sobrinus* were treated with an undiluted sodium bicarbonate-based powdered dentifrice containing 0.22 percent sodium fluoride. Results of this study indicated a 47-percent reduction in cavities as compared to the control group. This reduction in cavities was not statistically different from the 43-percent reduction in total cavities obtained by topical treatment with an undiluted sodium bicarbonate-based toothpaste containing the same level of sodium fluoride.

The comment also submitted several clinical studies that evaluated the anticaries effectiveness of fluoridated and nonfluoridated powdered dentifrices. However, the studies involving nonfluoridated powdered dentifrices were not related to and do not support the effectiveness of the comment's dentifrice product that contains sodium fluoride as the active ingredient.

The comment submitted a 1-year clinical study (Ref. 5) that demonstrated the anticaries effectiveness of tooth powders containing fluorapatite (essentially calcium fluoride). Although the powdered dentifrice used in this study contained an active ingredient

(fluorapatite) different than the active ingredient found in the comment's sodium fluoride dentifrice product, the study supported the anticaries effectiveness of a powdered dentifrice dosage form. In this study, 150 medical students brushed daily with one of three dentifrices containing: (1) 71.4 percent fluorapatite, (2) an ion-free "synthetic apatite" consisting of hydroxyapatite with a surface layer of fluorapatite (total fluorine content, 0.25 percent), or (3) a control powdered dentifrice not containing fluoride. Results of this study indicated that the group that brushed with the fluorapatite powder and the group that brushed with the "synthetic apatite" paste developed an average of 38 and 67 percent fewer cavities, respectively, than those students who brushed with the nonfluoride tooth powder.

Another study (Ref. 6) compared human enamel uptake of fluoride from a sodium fluoride/sodium bicarbonate dentifrice in a powdered and a paste dosage form. In this study, human enamel was ground and polished flat to provide a uniform surface and then demineralized to create a simulated white-spot caries lesion. Several enamel slabs were exposed continuously for 30 minutes at body temperature to a tooth powder (with a poured-bulk density of 1.0 to 1.2 g/milliliter (mL) and available fluoride ion concentration equal to or greater than 850 ppm) and a toothpaste containing sodium fluoride/sodium bicarbonate with an available fluoride ion concentration equal to or greater than 650 ppm. Results of this study indicated that both the powder and paste dosage forms demonstrated comparable enamel uptake of fluoride ions.

The comment concluded by stating that the data demonstrate the safety and effectiveness of a powdered dentifrice containing sodium fluoride and show that such a product can provide effectiveness equivalent to a toothpaste containing a similar abrasive system. The comment urged the agency to include sodium fluoride/sodium bicarbonate powdered dentifrices in the final monograph for OTC anticaries drug products.

The agency has reviewed the data provided by the comment and determined that sufficient data have been provided to generally recognize as safe and effective powdered dentifrices containing sodium fluoride with a sodium bicarbonate abrasive. However, the agency points out that several of the studies submitted measured the anticaries effectiveness of dentifrices containing active agents (fluorapatite, carbamide-urease, and fluoridated table

salt) different than the active ingredient contained in the comment's tooth powder (sodium fluoride). Although the data from one study provide some indication of cariostatic effectiveness of a fluorapatite dentifrice, the agency does not find these studies pertinent to the determination of the safety and effectiveness of the comment's sodium fluoride/sodium bicarbonate powdered dentifrice.

The agency considers the biological studies submitted by the comment as demonstrating that the bioequivalence and bioavailability of fluoride ions are comparable for sodium fluoride/sodium bicarbonate powdered and paste dentifrices containing the same concentration of theoretical total fluorine. Results of several well-designed animal caries studies (Refs. 2, 3, and 4) demonstrate that rats inoculated with cariogenic bacteria and fed a caries promoting diet developed 42 to 51 percent fewer cavities when treated with a topical application of sodium fluoride/sodium bicarbonate powdered dentifrice than rats in a control group. In addition, the agency concludes that the results of the submitted human enamel uptake study (Ref. 6) indicate that the measured human enamel uptake of fluoride from a powder containing sodium fluoride/sodium bicarbonate with a fluoride ion concentration of 1,000 ppm was better than the fluoride uptake of a similar dentifrice paste formulation. Although the agency does not believe that this system is comparable to real-life development of early dental caries or that a one-time exposure of enamel slabs continually for 30 minutes at 37 °C simulates real-life conditions of short, intermittent exposures during a month's usage, the agency does believe that fluoride uptake is a marker of potential anticaries effectiveness and considers the two fluoride dosage forms at least equivalent.

Accordingly, the agency is including sodium fluoride/sodium bicarbonate powdered dentifrices in § 355.10(a)(2) of this final monograph as follows:

Dentifrices containing 850 to 1,150 ppm theoretical total fluorine in a powdered dosage form: Sodium fluoride 0.188 to 0.254 percent with an available fluoride ion concentration of \geq 850 ppm for products containing the abrasive sodium bicarbonate and a poured-bulk density of 1.0 to 1.2 grams per milliliter.

References

- (1) Comment No. C00066, Docket No. 80N-0042, Dockets Management Branch.
- (2) Tanzer, J. M. et al., "Effects of Bicarbonate-based Dental Powder, Fluoride, and Saccharin on Dental Caries and on *Streptococcus sobrinus* Recoveries in Rats,"

Journal of Dental Research, 66(3):791-794, March, 1987.

(3) Tanzer, J. M. et al., "Bicarbonate-based Dental Powder, Fluoride, and Saccharin Inhibition of Dental Caries Associated with *Streptococcus mutans* Infection of Rats," *Journal of Dental Research*, 67(6):969-972, June, 1988.

(4) McMahon, T. et al., "Caries Inhibition by Bicarbonate-based Dental Powder in *S. mutans* 10449S-infected Rats," *Journal of Dental Research*, 67:343, 1988.

(5) McClendon, J. F., and W. C. Foster, "Prevention of Dental Caries by Brushing The Teeth With Powders Containing Fluorapatite," *Journal of Dental Research*, 26:233-239, 1947.

(6) Letter from J. J. Hefferen, J. J. Hefferen Resources, Inc., to T. Winston, Church & Dwight Co., Comment No. C00066 (Attachment 1), Docket No. 80N-0042, Dockets Management Branch.

14. One comment responded to the agency's concern expressed in the tentative final monograph (53 FR 22430 at 22444) that several possible methods of applying a powdered dosage form to a toothbrush may lead to significant variations of fluoride ion delivered to the teeth. The comment agreed that directions for using powdered products have been varied. However, the comment indicated that this is not a reason to determine that a sodium fluoride powdered dentifrice would not be safe and effective. The comment added that after several years of marketing a powdered dentifrice, it has found that pouring a powdered dentifrice from a container with a flip-top spout provides a cleaner and simpler application of the product with a uniform dosage of fluoride.

The comment claimed that the available fluoride ion obtained from two applications of a tooth powder containing a minimum of 850 ppm soluble (available) fluoride ion will be equal to or greater than the Panel's recommended 650 ppm available fluoride ion for sodium fluoride dentifrices. The comment based the need for two applications of tooth powder on its recommendation that sodium fluoride/sodium bicarbonate powdered dentifrices have a poured-bulk density of 1.0 to 1.2 g/mL and an available fluoride ion concentration equal to or greater than 850 ppm. The comment responded to several concerns raised by the agency in the tentative final monograph (53 FR 22430 at 22443). These concerns involved previous recommendations that two poured-bulk density ranges (0.5 to 0.99 g/mL and 1.0 to 1.7 g/mL) were necessary for powdered fluoride dentifrices and that two applications per brushing with a powdered dentifrice in the lower poured-bulk density range would provide an appropriate dose of

fluoride. The comment stated that the two poured-bulk density ranges were based on the assumption that equal volumes of tooth powder and toothpaste are applied in a single application to the brush; however, that assumption may no longer be correct because of the difference in consistency of the two dosage forms. The comment mentioned that more toothpaste than tooth powder can be applied to a brush without falling off; thus, the level of fluoride delivered to the teeth in one application is greater with a toothpaste than with a tooth powder, assuming comparable theoretical total fluorine.

The comment submitted a study (Ref. 1) that measured the weight of tooth powder and toothpaste applied in a single application to a toothbrush. Subjects were instructed to generously pour tooth powder onto a wet toothbrush so that the bristles were completely covered. The subjects were also instructed to apply to a similar size brush an amount of toothpaste they would normally use during brushing. The weight of dental powder in a single application was determined by weighing the toothbrush (plus a piece of paper used to catch spillage) before and after application; whereas the weight of the toothpaste was determined by weighing the package before and after applying a single dose to a toothbrush. The results of this study indicated that consumers applied an average of 0.8 g of powdered dentifrice and 1.46 g of paste to the same type of toothbrush. Results of this study indicated that two applications of a powdered dentifrice product of poured-bulk density 1.1 g/mL provides a level of fluoride comparable to a single application of a fluoridated toothpaste containing the same fluoride concentration.

The data were further analyzed (Ref. 2) to determine what dosage of fluoride would be provided if two applications of tooth powder with an available fluoride concentration of 850 to 1,100 ppm were placed on a toothbrush. The comment stated that, assuming two applications of tooth powder and one of toothpaste, the extrapolated amount of available fluoride ion delivered to the teeth by the tooth powder is comparable to the amount of soluble fluoride ion provided by a toothpaste. Based on these data, the comment recommended that the directions specify two applications of fluoride powder dentifrices containing 850 to 1,100 ppm theoretical total fluorine and a poured-bulk density range of between 1.0 and 1.2 g/mL.

One comment discussed directions for use of powdered fluoride dentifrices by children under 12 years of age. In the

tentative final monograph (53 FR 22430 at 22444), the agency had stated that children under 12 years of age may require greater manual dexterity to properly use a powdered dentifrice than is needed to correctly use a toothpaste. The agency expressed concern about the potential for young children to accidentally consume a toxic amount of fluoride when using a tooth powder compared to a toothpaste. The comment contended that powdered dentifrices do not pose any greater risk over pastes for accidental overdoses by children. The comment added that, while it believes that children between 6 and 12 years of age can use a powdered dentifrice properly, it has no objection to the monograph providing that powdered dentifrices not be labeled for use by children under 6 years of age and requiring labeling that states use by children 6 to under 12 years of age should be only with adult supervision. However, the comment expressed concern that such labeling might give the false impression that there is an inherent unsafe quality with the product, rather than merely a difficulty for children to use the product properly. The comment suggested the monograph include the following directions and labeling for powdered fluoride dentifrices to prevent any such false impressions: "Since a powdered fluoride dentifrice may be difficult for children to use, this product is not recommended for children under 6. Children between the ages of 6 and 12 should use this product under adult supervision."

The agency has reviewed the data (Refs. 1 and 2) and determined that the directions for use of fluoride powdered dentifrices with a poured-bulk density of 1.0 to 1.2 g/mL and an available fluoride ion concentration equal to or greater than 850 ppm must specify two applications to deliver a comparable amount of fluoride as a fluoride toothpaste of the same strength. One study (Ref. 1) showed that in a single application 45 percent less tooth powder than toothpaste was applied to a similar size brush. Because spillage that occurred during the weighing procedure was included in the final applied weight of powder, even less tooth powder than toothpaste was actually placed on the brush. Thus, the agency agrees with the comment that consumers who use two applications of a fluoride tooth powder with a poured-bulk density of 1.0 to 1.2 g/mL containing 850 to 1,100 ppm available fluoride ion receive an amount of fluoride ion comparable to using a single application of a sodium fluoride

toothpaste with an available fluoride ion concentration equal to or greater than 650 ppm. Accordingly, the agency is including directions in this final monograph that provide for two applications of fluoride powdered dentifrices. The agency is also including in the LTP tables a poured-bulk density range of 1.0 to 1.2 g/mL for powdered dentifrices (see section I.F., comment 37 of this document).

Regarding the use of powdered fluoride dentifrices by children, the agency does not believe that powdered fluoride dentifrices pose a greater threat for accidental ingestion than fluoride toothpaste. Also, the agency does not believe that children 6 years of age and older are likely to consume a toxic amount of fluoride from a dentifrice powder. In most instances, such products will be used under adult supervision. Further, existing regulations (§ 310.201(a)(10)(iv)) establish package size limitations for sodium fluoride preparations.

The agency agrees with the comment that these products should not be labeled for use by children under 6 years of age, and should be labeled for use with adult supervision by children 6 to under 12 years of age. Accordingly, the agency is adding the following directions for powdered dentifrices in § 355.50(d)(1)(iii):

Powdered dosage form with a theoretical total fluorine concentration of 850 to 1,150 ppm identified in § 355.10(b)(2). Adults and children 6 years of age and older: Apply powder to a wet toothbrush; completely cover all bristles. Brush for at least 30 seconds. Reapply powder as before and brush again. Rinse and spit out thoroughly. Brush teeth, preferably after each meal or at least twice a day, or as directed by a dentist or doctor. Instruct children under 12 years of age in good brushing and rinsing habits (to minimize swallowing). Supervise children as necessary until capable of using without supervision. Children under 6 years of age: Do not use unless directed by a dentist or doctor.

The agency believes that these directions will not give consumers a false impression that there is any inherent unsafe quality with these products.

References

- (1) J. Ross Associates, "A Dentifrice Use Test," draft of unpublished study, Comment No. C00066 (Attachment I, Exhibit 5), Docket No. 80N-0042, Dockets Management Branch.
- (2) J. Ross Associates, "A Dentifrice Use Test," draft of unpublished study, Comment No. C00066 (Attachment I, Exhibit 7), Docket No. 80N-0042, Dockets Management Branch.

15. One comment agreed with the agency's concern expressed in the tentative final monograph (53 FR 22430 at 22444) that proper packaging is

important to prevent moisture contamination of a powdered dentifrice, particularly in areas where the humidity is high due to showering and bathing. The comment indicated that its powdered dentifrice product is sold in a plastic bottle with a flip top cap and, therefore, quite effectively prevents moisture contamination.

As discussed in the tentative final monograph (53 FR 22444), the agency agrees with the comment that powdered fluoride dentifrices would probably remain more stable for a longer period of time than the paste form because there would be less interaction between dry ingredients during storage of the dentifrice. However, the agency recognizes that the storage conditions of a powdered fluoride dentifrice would have a significant impact on whether the product would remain stable longer than the paste form. Storage of the powdered product in areas where the humidity is high due to showering and bathing would require that the container be resistant to moisture contamination.

A "tight container," as defined in the United States Pharmacopeia (U.S.P.), would meet this criterion. The U.S.P. defines a "tight container" (Ref. 1) as a container that "protects the contents from contamination by extraneous liquids, solids, or vapors, from loss of the article, and from efflorescence, deliquescence, or evaporation under the ordinary or customary conditions of handling, shipment, storage, and distribution, and is capable of tight reclosure."

In addition, § 211.94 (21 CFR 211.94) of the FDA current good manufacturing practice (GMP) regulations addresses drug product containers and closures. Section 211.194(a) states: "Drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements." Section 211.194(b) states: "Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product."

Therefore, based on § 211.94 of the FDA GMP regulations and the U.S.P. standard for a "tight container," the agency is adding a new paragraph in § 355.20(b) that reads: "*Tight container packaging.* To minimize moisture contamination, all fluoride powdered dentifrices shall be packaged in a tight container, which is defined as a container that protects the contents from contamination by extraneous liquids, solids, or vapors, from loss of the article, and from efflorescence, deliquescence,

or evaporation under the ordinary or customary conditions of handling, shipment, storage, and distribution, and is capable of tight reclosure."

Reference

(1) *The United States Pharmacopeia 23—The National Formulary 18*, United States Pharmacopeial Convention, Inc., Rockville, MD, p. 10, 1994.

C. Comments on Labeling of OTC Anticaries Drug Products

16. One comment responded to the agency's question whether consumers would benefit in having OTC fluoride-containing drug products labeled to state their fluoride levels. The comment objected to fluoride level labeling for OTC anticaries drug products and provided the results of a consumer survey as support (Ref. 1). The survey was conducted in shopping malls in eight different geographic areas and included a sample of 200 women between the ages of 18 and 49. The women routinely purchased dentifrice products for their households. In addition, 150 women with children between 1 and 5 years of age were interviewed to determine the habits and practices of women with children regarding the use of fluoride dentifrices. The comment stated that the results of the survey indicate that: (1) Consumers believe that fluoride in dentifrice products is important in preventing cavities, (2) regardless of the unit of measurement, e.g., ppm, percent, or milligrams per inch (mg/in), used to label the fluoride concentration, consumers believe "more is better" when choosing a dentifrice because they consistently selected dentifrices labeled with the higher net fluoride, indicating that consumers believe that there are differences in the effectiveness of fluoride dentifrice products, (3) most consumers know how to use fluoride dentifrices, (4) most consumers are aware of the fluoride ingredient in the toothpaste, and (5) most parents take an interest in and supervise their children's brushing habits. Based on these results, the comment concluded that labeling fluoride-containing products to state their fluoride levels is not useful to consumers and could be misleading. The comment recommended that such labeling not be required for OTC fluoride drug products.

The agency has evaluated the consumer survey and determined that it has some methodology deficiencies. The major deficiency is an inadequate respondent sample size. In order to generalize the findings of this study to the general population, it would be necessary to have a larger number of

respondents. Further, the survey involved only women between the ages of 18 and 49 years of age. There were no men in the survey nor women above 49 years of age; these people might also have reasons for wanting to know the fluoride content. In addition, the survey did not attempt to assess the relative understanding by the respondents of the various methods of expressing quantities of fluoride. Contextual material could have been used to clarify the meaning of the measures used, making it more likely that consumers could make use of the information provided, regardless of the type of measurements used.

Nonetheless, the survey provides some useful information. It demonstrates that more consumers chose a dentifrice labeled with the higher net fluoride content, based on the concept that "more fluoride is better." Rather than emphasizing fluoride concentration numbers, the agency believes that labeling would be more beneficial if it informs consumers who have a greater propensity to develop cavities of the need to use a higher strength fluoride dentifrice. Therefore, in this final rule, the agency is including in § 355.50(f)(2) the following optional additional labeling statement for dentifrice products containing 1,500 ppm theoretical total fluorine: "Adults and children over 6 years of age may wish to use this extra-strength fluoride dentifrice if they reside in a nonfluoridated area or if they have a greater tendency to develop cavities." Because of concerns about dental fluorosis occurring in children under 6 years of age, the agency is requiring extra-strength fluoride dentifrice products to state in their labeling that the product should not be used by children under 6 years of age unless directed by a doctor or dentist. (See section I.B., comment 10 of this document.)

In conclusion, no comments, data, or information were submitted in support of fluoride level labeling. Accordingly, this final monograph does not contain a requirement that fluoride-containing dentifrice products label the quantity of fluoride. However, it does provide an optional additional labeling statement that manufacturers may use for these products.

Reference

(1) Comment No. C0097, Docket No. 80N-0042, Dockets Management Branch.

17. One comment objected to the inclusion of the term "treatment" as the single recommended term in the proposed statement of identity in § 355.50(a). The comment stated that the

terms "treatment" and "dental" are both appropriate statements of identity for various anticavity product dosage forms and that other equally truthful and nonmisleading identifiers are also appropriate. The comment made two recommendations: (1) The term "treatment" be retained as an optional statement of identity for gels, rinses, concentrated rinses, rinse powders, or rinse effervescent tablets, and (2) the term "dental" also be listed as optional, such as in connection with a professionally promoted "dental treatment gel." The comment concluded that its suggested revisions to § 355.50(a) would provide for truthful and accurate statements of identity.

Another comment suggested that the agency delete the term "treatment" from the statement of identity and permit "anticavity dental rinse" or "fluoride dental rinse" as a statement of identity, because the term "treatment" does not appropriately describe the activity of these products. The comment stated that these rinse products provide their anticaries benefits primarily through a prophylactic mode of action and are perceived by consumers as preventive prophylactic measures rather than therapeutic treatments. The mechanism of fluoride action is well recognized in the scientific community and was addressed in the Panel's report (45 FR 20666 at 20672). According to the comment, the Panel noted that fluoride increases enamel resistance to acid solubility, making the teeth less susceptible to plaque acid attack, thereby producing its cariostatic effect. The comment concluded this is primarily a preventive mode of action as contrasted to a therapeutic action. The comment thus proposed that the agency delete the term "treatment" from the statement of identity and permit "anticavity dental rinse" or "fluoride dental rinse" as a statement of identity. The comment concluded that these statements of identity are more descriptive and meaningful to consumers and more accurately define the therapeutic benefit of an anticaries drug product.

The agency discussed the use of the term "treatment" as part of the statement of identity for nonabrasive gels and rinses in the tentative final monograph (50 FR 39854 at 39866) in response to a comment that pointed out that some current dentifrice (abrasive-containing) products are transparent or translucent and are called gels by manufacturers and consumers. Two other comments also expressed concern that the use of the term "gel" alone for a nonabrasive 0.4-percent stannous fluoride product could be confusing to

the consumer in distinguishing between abrasive and nonabrasive fluoride gels; these comments suggested the term "nonabrasive dental gel." The agency agreed with the comments that it is important to provide labeling that would allow consumers to easily distinguish between a nonabrasive and an abrasive-containing fluoride gel, but stated that the term "nonabrasive" may not be meaningful for consumers. The agency also stated that because nonabrasive fluoride gels had not been widely marketed, consumers were not familiar with the use of the term "dental gel" to identify such products, particularly in the context of widely marketed abrasive-containing fluoride dentifrices labeled as gels. Thus, the agency proposed that the term "treatment" be included in the statement of identity for all nonabrasive OTC fluoride products to clearly distinguish between a dentifrice and a nonabrasive fluoride product.

The agency agrees with the comment that the term "treatment" can be optional for fluoride dental rinses, but disagrees with making this term optional for nonabrasive fluoride gels. As discussed in section I.A., comment 7 of this document, the agency has added the word "preventive" to the definition of a "treatment gel." The comments did not discuss the possibility that consumers could be confused in distinguishing a nonabrasive fluoride treatment gel from an abrasive-containing dentifrice gel. The comment also did not explain how such labeling would distinguish a nonabrasive fluoride gel from an abrasive fluoride dentifrice. In order for consumers to be better able to make this distinction, the agency is requiring that the term "preventive treatment" be included in the statement of identity for nonabrasive fluoride gels. Because a distinction is not needed for fluoride dental rinses, the agency is providing that the phrase "preventive treatment" be optional in the statement of identity for these products. The statement of identity for OTC anticaries drug products in § 355.50(a) of this final monograph reads as follows:

The labeling of the product contains the established name of the drug, if any, and identifies the product as the following: "anticavity fluoride" (select one of the following as appropriate: "dentifrice," "toothpaste," "tooth polish," "tooth powder;" (optional: "dental") "preventive treatment gel;" or (optional: "preventive treatment" or "dental")) (select one of the following: "rinse," "concentrated solution," "rinse powder," or "rinse effervescent tablets"). The word "mouthwash" may be substituted for the word "rinse" in this statement of identity if the product also has

a cosmetic use, as defined in section 201(i) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(i)).

18. One comment requested revisions in the proposed statement of identity for fluoride-containing products in § 355.50(a). The comment contended that a fluoride-containing liquid product labeled both to prevent cavities and to freshen the breath should be identified as an "anticavity or fluoride mouthwash," whereas a fluoride rinse that makes no cosmetic claims should properly be identified as an "anticavity or fluoride rinse."

Several other comments requested that the statement of identity for anticaries drug products include the terms "tooth powder" and "tooth polish." The comments stated that these terms are commonly recognized and have been used in dentifrice product labeling for many years.

The agency agrees that a fluoride-containing liquid product represented both to prevent cavities and to freshen the breath can properly be identified as an "anticavity or fluoride mouthwash." Further, the agency agrees that a fluoride rinse with no cosmetic claims in its labeling is appropriately identified as a "rinse." The agency also agrees that the terms "tooth polish" and "tooth powder" are suitable for use as part of the statement of identity for anticaries drug products. The word "tooth" indicates the site of usage; "powder" is a dosage form; and "polish" has been used in labeling of these products for many years without consumer confusion. The word "polish" indicates a cosmetic usage. As discussed in comment 19, the agency's OTC drug regulations do not prohibit placing a cosmetic statement of identity of a drug/cosmetic product on the principal display panel. Accordingly, the agency is including the terms "mouthwash" (if the product also has a cosmetic use), "tooth polish," and "tooth powder" in § 355.50(a) in this final rule. (For further discussion of the statement of identity, see section I.C., comments 17 and 19 of this document.)

19. Two comments noted that many anticaries drug products also properly contain cosmetic ingredients and include cosmetic labeling. The comments contended that manufacturers must be permitted to label such products with statements of identity that include truthful drug/cosmetic terminology. For example, the comments stated that the same product may be used both as an anticaries dentifrice and as a cleaning and breath freshening toothpaste. The comment maintained that such a product should be able to truthfully declare in its

statement of identity what it is and what it does.

One comment maintained that the agency's labeling policy set forth in a proposal to amend the statement of identity requirements for OTC drugs published in the *Federal Register* of April 17, 1986 (51 FR 13023), along with the agency's exclusivity and label separation policies, make it impossible for a manufacturer to comply with both the drug and cosmetic labeling requirements set forth in the statute and regulations. The comment pointed out that existing FDA regulations require that the statement of identity for both drug and cosmetic products appear on the principal display panel of the product. The comment contended that the effect of the agency's drug-cosmetic label separation policy is that the cosmetic statement of identity may not be placed on the principal display panel.

The comment argued that cosmetic terminology should be allowed anywhere in the labeling of an anticaries dentifrice that is also a cosmetic product so long as it does not render the product's labeling false or misleading. The comment argued that consumers would not be misled by the inclusion of both kinds of labeling on an anticaries drug product. On the contrary, the comment stated that consumers would more likely be misled if the drug and cosmetic statements of identity and other claims were to appear on entirely different portions of the label. The comment concluded that there is no legal or policy justification for this label separation policy.

If a product covered by this rulemaking is marketed for both drug and cosmetic use, it must conform to the requirements of the final OTC drug monograph and bear appropriate labeling for cosmetic uses in accord with section 602 of the act (21 U.S.C. 362) and the provisions of 21 CFR parts 701 and 740.

Sections 201.61 and 701.11 of the CFR require that the statement of identity for OTC drug and cosmetic products each appear on the principal display panel of the product. The agency's OTC drug regulations do not prohibit placing the cosmetic statement of identity of a drug/cosmetic product on the principal display panel. However, in accordance with the revised labeling requirements for OTC drug products, cosmetic claims may not appear within the boxed area designated "APPROVED USES." (See section I.A., comment 1 of this document.) As discussed in the final rule on the agency's "exclusivity policy" (51 FR 16258 at 16264 (paragraph 14)), cosmetic terminology is

not reviewed and approved by FDA in the OTC drug monographs and therefore can not be placed in the boxed portion of the label. Cosmetic terminology can, however, be placed outside the box and on the product's principal display panel. In addition, cosmetic claims may appear elsewhere in the labeling should manufacturers choose the labeling alternative provided in § 330.1(c)(2)(i) or (c)(2)(iii) for labeling drug/cosmetic products. Although the agency does not specifically prohibit commingled drug and cosmetic labeling other than in the product's indications section, such claims should be appropriately described so that consumers will be readily able to differentiate the drug aspects from the cosmetic aspects of such labeling. If commingled drug and cosmetic labeling claims are confusing or misleading, the product's labeling could be misleading within the meaning of sections 502(a) and 602(a) of the act (21 U.S.C. 352(a) and 362(a)).

20. One comment objected to the first portion of the agency's proposed additional labeling statement for fluoride dental rinses in § 355.50(e)(2), which states: "This is a(n)" (select one or both of the following: "anticavity" or "fluoride") "treatment rinse, not a mouthwash. Read directions carefully before using." The comment contended that a properly formulated and labeled product could be legally and accurately promoted as both an anticavity dental rinse and a cosmetic mouthwash. The comment added that requiring the "not a mouthwash" statement on fluoride dental rinses is not consistent with the agency's well-established policy regarding OTC drugs that claim both therapeutic and cosmetic benefits. The comment stated that dual drug/cosmetic labeling is permitted in other product categories (e.g., antiperspirants, dentifrices, and antidandruff shampoos), and that the agency does not require similar labeling statements for such products. The comment contended that requiring an anticavity dental rinse/mouthwash product to display the "not a mouthwash" labeling statement is inconsistent with agency policy for these other OTC products and could be confusing to consumers who have been receiving both benefits from previous use of these products.

The comment argued that the agency's proposal would adversely affect the truthful promotion of OTC anticavity dental rinses, and that consumers desiring both anticavity and breath freshening activity would have to purchase two separate products (i.e., an anticavity dental rinse and a cosmetic mouthwash) instead of purchasing one product that would provide both

benefits. The comment requested the agency to delete the statement in proposed § 355.50(e)(2) that says "This is a(n)" (select one or both of the following: "anticavity" or "fluoride") "treatment rinse, not a mouthwash."

In the tentative final monograph for OTC anticavity drug products, the agency expressed concern that, because fluoride dental rinses and cosmetic mouthwashes are similar in appearance, consumers might confuse such products (50 FR 39854 at 39869). The agency stated that proper labeling is an important aid to preventing consumer confusion as to the use of these products. Therefore, the agency proposed labeling, including the labeling statement " * * * not a mouthwash * * * " in § 355.50(e)(2), to minimize confusion and to help consumers distinguish between dental rinses and cosmetic mouthwashes.

The agency sees no reason why an appropriately labeled OTC fluoride rinse cannot also be used for freshening the breath. Such a product can properly be identified as an anticavity or fluoride rinse or mouthwash (see section I.C., comment 18 of this document). However, the agency believes that proper labeling of OTC fluoride rinses is an important factor in helping to ensure the safe and effective use of these products.

The agency is concerned that, based upon familiarity with cosmetic mouthwash use, a consumer might overuse and/or misuse an OTC fluoride rinse. For example, directions for use of fluoride rinses are notably different from directions for use of cosmetic mouthwashes. Cosmetic mouthwashes are often labeled for multiple use during the day (e.g., "first thing in the morning, after meals, and before social engagements") (Ref. 1). Fluoride rinses are labeled for use once or twice a day (§ 355.50(d)(2)). Cosmetic mouthwash labeling directs consumers to "rinse or gargle 30 seconds" (Ref. 1). The directions for use of fluoride rinses state that consumers should " * * * swish * * * between your teeth for 1 minute * * * Do not eat or drink for 30 minutes after rinsing" (§ 355.50(d)(2)).

Based on the above discussion, the agency has determined that the "not a mouthwash" statement need not be required labeling for OTC fluoride rinses. Accordingly, the agency is not including proposed § 355.50(e)(2) in this final monograph. However, in order to maximize the safe and effective use of OTC fluoride rinses, the agency concludes that these products must contain labeling that clearly instructs consumers to read the directions. The agency also believes that this

information should be displayed on the principal display panel. Therefore, the agency is including in this final monograph new § 355.55 as follows: "Principal display panel of all fluoride rinse drug products. In addition to the statement of identity required in § 355.50, the following statement shall be prominently placed on the principal display panel: 'IMPORTANT: Read directions for proper use'."

Reference

(1) Labeling for Scope®, OTC Vol. 08AFM, Docket No. 80N-0042, Dockets Management Branch.

21. One comment disagreed that the heading "Indication" proposed in § 355.50(b) was needed in the labeling of OTC fluoride dentifrice products. The comment contended that the function of a fluoride toothpaste is generally known, and consumers have safely and correctly used these products for years without the heading "Indication" in the labeling of these products. The comment added that the consuming public probably does not consider fluoride toothpaste to be a drug in the same sense as other common OTC drug products; thus, consumers could be confused by this new labeling requirement. The comment suggested that § 355.50(b) be revised to make use of the heading "Indication" optional.

The agency does not agree that the heading "Indication(s)" should be optional. All OTC drug monographs in parts 331 through 358 (21 CFR 331 through 358) have been promulgated with a standard "Indications" paragraph requiring that the labeling of the product state its FDA approved use(s) under the heading "Indication(s)." However, two general OTC drug product labeling provisions, which were promulgated after the comment was submitted, provide alternatives. Section 330.1(c)(2)(i) provides that, at the option of the manufacturer, the "Indications" may be designated "APPROVED USES" or given a similar designation as permitted in that paragraph of the regulations. Section 330.1(i)(8) provides that "indications" or "uses" may be used interchangeably.

Although the comment claims that consumers may not be accustomed to reading such information on dentifrice product labels, the agency believes that consumers should be aware that these products are drugs. This same principle would apply to other OTC products that consumers might not consider to be drugs because they have not contained such labeling in the past, e.g., antiperspirants and sunscreens. The comment did not provide any evidence that consumers would be confused by

reading this type of labeling, which has appeared for years on many widely used OTC drug products. The agency finds that informative headings such as "Indications" or "Uses" (as well as "Warnings" and "Directions") are useful to consumers and provide uniformity to OTC drug product labeling. Therefore, the agency is not making use of the heading "Indication(s)" optional.

22. One comment noted that § 330.1(g) (21 CFR 330.1(g)) requires that all drugs, unless exempted, be labeled with the warning "Keep this and all drugs out of the reach of children." The comment stated that OTC anticaries dentifrices and rinses obviously should not be subject to the general warning because they bear directions for use by children. The comment requested that OTC anticaries drug products be exempted from the requirement to bear this warning.

The agency agrees, in part, with the comment. The agency recognizes that fluoride dentifrices are generally kept within the reach of children to encourage use on a regular basis. The agency is concerned that the general warning "Keep this and all drugs out of the reach of children" could discourage or inhibit parents from keeping fluoride dentifrices within easy reach of children 6 years of age and older who are able to use dentifrice products safely and effectively. However, these products should not be within easy reach of children under 6 years of age, who should be supervised and instructed in the proper use of these products and who are vulnerable to dental fluorosis. Thus, in § 355.50(c) of this final monograph, the agency is modifying the § 330.1(g) warning to read as follows for fluoride dentifrice products: "Keep out of the reach of children under 6 years of age."

The agency disagrees with the comment with respect to fluoride rinses and gels. The agency believes that these dosage forms should not be within easy reach of any children. These products are not indicated for use in children under 6 years of age on an OTC basis. For children 6 to under 12 years of age, the products must be labeled for use under the supervision of an adult. These fluoride dosage forms are potentially more toxic than fluoride dentifrice products because they do not contain an abrasive that can bind some of the fluoride ion and because a child under 6 is more likely to drink a flavored liquid than eat large amounts of toothpaste, which may contain up to 40 percent by weight of inert abrasive ingredients.

The agency has reviewed its adverse reaction data base covering the period

from 1985 to 1992 for reports related to fluoride rinses, gels, and dentifrices (Ref. 1). In the 0- to 9-year age group, there were 22 reports for fluoride rinses and gels, but no reports for fluoride dentifrice products. In addition, the agency has reviewed available data concerning exposures to fluoride toothpastes and fluoride rinses (mouthwash) in annual reports of the American Association of Poison Control Centers for the years 1989 to 1991 (Refs. 2, 3, and 4). For children under 6 years of age, the number of accidental exposures averaged approximately 1,200 per year for fluoride toothpastes and almost 1,000 per year for fluoride rinses. However, fluoride toothpaste usage is estimated to be 300 times that of fluoride rinses. Thus, the accidental ingestion rate for fluoride toothpaste is much lower than for fluoride liquid products. Therefore, the available data strongly support a requirement that fluoride rinses and gels be labeled in accord with the general warning in § 330.1(g), without any modifications. This requirement appears in § 355.50(c)(2) of this final monograph.

References

- (1) Food and Drug Administration, Center for Drug Evaluation and Research, Adverse Reaction Summary Listing for Fluoride Rinses, Gels, and Dentifrices for years 1985 to 1992, OTC Vol. O8AFM, Docket No. 80N-0042, Dockets Management Branch.
- (2) Litovitz, T. L. et al., "1989 Annual Report of the American Association of Poison Control Centers National Data Collection System," *The American Journal of Emergency Medicine*, 8:421, 1990.
- (3) Litovitz, T. L. et al., "1990 Annual Report of the American Association of Poison Control Centers National Data Collection System," *The American Journal of Emergency Medicine*, 9:488, 1991.
- (4) Litovitz, T. L. et al., "1991 Annual Report of the American Association of Poison Control Centers National Data Collection System," *The American Journal of Emergency Medicine*, 10:480, 1992.

23. Two comments disagreed with the directions proposed in § 355.50(d)(1) for anticaries dentifrices, which state: "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." The comments disagreed in two major areas: (1) The agency's reference to brushing at least once daily may be misinterpreted by the public as being adequate and, therefore, may lead to less brushing and poor oral health care. The comments indicated that there is no clear consensus within the dental profession as to the number of times teeth should be brushed each day. Many dentists recommend brushing after each

meal, and, for reasons of practicality, brushing at least twice a day—after breakfast and in the evening. The comments indicated that they are unaware of any data that suggest brushing once a day is adequate, and therefore urged the agency not to refer to any minimum number of times for brushing. (2) The contraindication for the use of fluoride dentifrices by children under 2 years of age is unwarranted because children that age have many teeth requiring anticaries protection. The comments stated that early instruction of children regarding dental care minimizes the risk of fluorosis due to ingestion of fluoride dentifrice and encourages good oral health care habits.

The Panel reviewed several clinical studies that showed fluoride-containing dentifrices effectively increase resistance to enamel solubility and therefore reduce dental decay when applied to the teeth at least once a day (Refs. 1, 2, and 3). Radike (Ref. 3) describes three 1-year clinical studies with a similar design conducted to determine whether the frequency of application affects the anticariogenic effect of a stannous fluoride dentifrice. Each study used similar stannous fluoride dentifrices, but the subjects (school children) were assigned one of three different brushing procedures: (1) Unsupervised brushing, (2) supervised brushing once-a-day after the noon meal, and (3) supervised brushing three times a day (after breakfast and dinner and before retiring). Each brushing regimen was assigned approximately the same number of control subjects as test subjects. Subjects in a control group assigned to a specific brushing procedure brushed with a nonfluoride-containing dentifrice. In the study in which no toothbrushing instructions were given and the subjects were allowed to follow their usual brushing habits, the fluoride dentifrice subjects developed 23 percent fewer new caries than those in the control group. In the study with one supervised brushing in the school room after the noon meal, the fluoride dentifrice subjects developed 34 percent fewer caries than those in the control group. In the third study with supervised brushing three times a day (after breakfast and dinner and before retiring), the fluoride dentifrice subjects developed 57 percent fewer new caries than those in the control group. The results from these studies clearly suggest that simply cleansing the teeth with an abrasive containing nonfluoridated dentifrice is not as effective in reducing the incidence of caries as brushing with a fluoride-

containing dentifrice. The data also show that more frequent topical applications of fluoride significantly enhance anticaries protection. Supervised brushing with a fluoride dentifrice once-a-day after the noon meal resulted in 33 percent fewer cavities than unsupervised brushing. Further, subjects who brushed three times a day with a fluoride dentifrice experienced: (1) 40 percent fewer new cavities than those who brushed with a fluoride dentifrice only once-a-day, even under supervision, and (2) 60 percent fewer cavities than those whose brushing was unsupervised. The results of these three studies indicate that fewer caries occur as frequency of supervised brushing and brushing after meals is increased.

Several additional studies (Refs. 4 through 7) also indicate that brushing immediately after meals is the most favorable time to reduce the number of cariogenic bacteria from all tooth surfaces. Two review studies (Refs. 4 and 6) discussed the role nutrition plays in the etiology of dental disease. Both studies concluded that one preventative measure to effectively reduce the number of cariogenic bacteria present in the mouth is to brush thoroughly after each meal with a fluoride-containing dentifrice. Forty years ago, another study (Ref. 7) indicated that many dentists and health workers strongly recommend that toothbrushing be performed immediately after the ingestion of sugar-containing food if brushing is to be effective in reducing dental cavities. The study also included a clinical investigation evaluating the effectiveness of reducing dental cavities by brushing the teeth with one of three types of nonfluoridated dentifrices immediately after the ingestion of food. This report (Ref. 7) dealt with only one of the dentifrices, the neutral paste. Subjects in the experimental group were instructed individually to brush their teeth thoroughly within 10 minutes after each ingestion of food or sweets and, when brushing was not possible, to rinse the mouth thoroughly with water. Toothbrushes and dentifrice were supplied to all experimental subjects. Subjects in the control group were not supplied with dentifrices or brushes, but were instructed to continue their customary oral hygiene habits of brushing only on arising and before retiring, rather than after the ingestion of food. When this study was conducted in 1950, fluoridated toothpastes were not available in the marketplace; thus, the control subjects would not have used a fluoridated dentifrice as a part of their customary oral hygiene habits.

Clinical results after 1 year indicated that brushing thoroughly immediately after the ingestion of food resulted in a 63-percent reduction in caries activity in the experimental group when compared to the control group.

A more recent 1982 study (Ref. 8) reviewed the prevention control of oral diseases and recommended at least two daily brushings with a fluoride dentifrice as effective in reducing the incidence of dental cavities. The study further stated that because toothbrushing is intended to remove food debris and dental plaque from the teeth, brushing after meals and sweet snacks is commonly recommended in dental health messages to the public.

The agency agrees with the comments and with many dentists that brushing properly and thoroughly more often than once daily will promote better oral health care. Reducing cariogenic activity by brushing more often than once a day, particularly after meals, can be explained by the synergistic effect of the antienzymatic properties of fluoride (45 FR 20666 at 20672) along with the mechanical removal of food debris. The Panel recognized that three factors are necessary for caries to occur (45 FR 20666 at 20672): (1) The teeth must be susceptible to caries, (2) acid-producing bacteria of the mouth must colonize on the teeth, and (3) a substrate must be present for bacteria to proliferate and to produce acid for demineralization of the teeth. Effective anticaries protection is achieved by exposing the tooth enamel to fluoride ions and by the mechanical removal of dental plaque and food debris from tooth surfaces and gingival tissue areas. Both objectives are better accomplished by toothbrushing more often than once daily, preferably after meals. The mechanical removal of food debris from teeth and gingival areas decreases the availability of metabolized carbohydrate sources, which are required for caries development.

The agency agrees with the Panel that brushing with a fluoride-containing dentifrice at least once daily effectively renders the teeth less susceptible to dental cavities. The agency also recognizes, however, that anticaries protection could be enhanced by brushing more than once a day, preferably after each meal to remove the food particles that provide the substrate necessary for bacteria to proliferate and produce acid in the development of dental caries (Ref. 3). Therefore, the agency is revising part of the directions for all OTC fluoride dentifrices to read: " * * * brush teeth thoroughly, preferably after each meal or at least twice a day, or as directed by a dentist or doctor."

The agency disagrees with the comments suggesting that the contraindication for children under 2 years of age is unwarranted. Very young children cannot be expected to rationally interpret and consistently follow the instructions involving proper toothbrushing; nor do they have the manual dexterity to use the fluoride dentifrice product properly. Children under 2 years of age do not have control of their swallowing reflex and do not have the skills to expectorate the toothpaste properly (50 FR 39854 at 39867). Although the prevalence of dental caries is decreasing, some reports suggest the incidence of mild fluorosis (a permanent, mottled discoloration of the teeth) in young children is increasing in the United States due to the increase of fluoride in our food chain (Ref. 9). Excessive ingestion of fluoride by young children increases the risk of fluorosis during the critical time of anterior teeth development and can interfere with the successful development of other emerging teeth (Ref. 10). Toothbrushing for children under 2 years of age when teeth are first emerging may also cause minor injury to the soft tissue in the mouth. The agency recognizes that young children are most susceptible to mild fluorosis as a result of improper use and swallowing of a fluoride dentifrice product. Based on the above, the agency concludes that it is appropriate to include in the labeling of fluoride dentifrice drug products containing 1,000 ppm theoretical total fluorine the following sentence: "Children under 2 years of age: Consult a dentist or doctor." The agency is including this sentence in the directions in § 355.50(d)(1)(i) of this final monograph. The agency is also including a similar statement in the directions for dentifrices containing 1,500 ppm theoretical total fluorine for children under 6 years of age (see section I.B., comment 10 of this document).

References

- (1) Council on Dental Therapeutics, *Accepted Dental Therapeutics*, 37th ed., American Dental Association, Chicago, p. 303, 1977.
- (2) Council on Dental Therapeutics, "Evaluation of Super Stripe Toothpaste," *Journal of the American Dental Association*, 71:930-931, 1966.
- (3) Radike, A. W., "Current Status of Research on the Use of a Stannous Fluoride Dentifrice," in OTC Vol. 080099.
- (4) Massler, M., "Nutrition and Dental Decay," *Food and Nutrition News*, 39:1-4, 1968.
- (5) Nikiforuk, G., and J. B. MacDonald, "An Evaluation of Dentifrices in the Prevention of Dental Caries and Gingivitis," *Journal of the*

Canadian Dental Association, 21:557-565, 1955, Abstracted in *Dental Abstracts*, 1(4):227, 1956.

(6) Finn, S. B., and R. B. Glass, "Sugar and Dental Decay," *World Review of Nutrition and Dietetics*, 22:318-320, 1975.

(7) Fosdick, L. S., "The Reduction of the Incidence of Dental Caries. 1. Immediate Tooth-Brushing with a Neutral Dentifrice," *The Journal of the American Dental Association*, 40(2):133-143, 1950.

(8) Council on Dental Therapeutics, *Accepted Dental Therapeutics*, 39th ed., American Dental Association, Chicago, pp. 335-337, 1982.

(9) Leverett, D. H., "Fluorides and the Changing Prevalence of Dental Caries," *Science*, 217:26-30, 1982.

(10) Simard, P. L. et al., "The Ingestion of Fluoride by Young Children," *Journal of Dentistry for Children*, 56:177-181, 1989.

24. Three comments objected to the directions proposed in § 355.50(d)(1) for anticaries products marketed in a dentifrice dosage form (containing 1,000 ppm theoretical total fluorine), which states: "Children under 6 years of age should be supervised in the use of this product." The comments contended that this is the type of language that is customarily used for products or activities that are dangerous, thus the language is needlessly alarmist. The comments explained that "supervision" in this usage connotes watchfulness to prevent any action by the child that could lead to harm. The comments claimed that a parent reading this direction for use might infer that toothpaste has some dangerous hidden toxicity. The comments emphasized that the important point is that children should be trained how to brush their teeth so that they will obtain the desired benefit of toothbrushing without swallowing excessive amounts of toothpaste, which would increase their risk of fluorosis. One comment stated that the proposed labeling implies that even after good brushing habits are acquired, every toothbrushing event until age 6 should be supervised by a parent. The comments requested that the directions be revised to read: "Instruct children under 6 years of age in good brushing and rinsing habits as recommended by your dentist." The comments argued that implicit in the concept of instruction is supervision until the parent is satisfied that the child can follow the instruction correctly. The comments concluded that the term "instruction" rather than "supervision" provides the correct emphasis, provides useful guidance adequate to deal with the concern about fluorosis, and does so without stimulating unwarranted parental concern.

Another comment did not object to the term "supervised" in the direction

for dentifrices containing 1,000 ppm theoretical total fluorine, but requested the agency to expand § 355.50(d)(1) to read: "To prevent swallowing, children under 6 years of age should be supervised in the use of toothpaste (mouthrinse)." The comment stated that young children should be educated in the proper manner of toothbrushing so as to help enhance proper brushing technique as well as appropriate product use (i.e., using small portions and spitting the dentifrice out after use, rather than ingestion). The comment stated that the Council on Dental Therapeutics of the American Dental Association (ADA) has recently adopted this statement and directed its use on all labeling for Council-accepted fluoride-containing dentifrices and mouthwashes.

The agency agrees with the comments. The Panel recommended that fluoride dentifrices be labeled to indicate that children under 6 years of age should be supervised in the use of these products. In the tentative final monograph for OTC anticaries drug products (50 FR 39854 at 39867), the agency interpreted 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 agency did not intend that every toothbrushing event until age 6 should be supervised. As the comments suggested, the important point is for parents to assure themselves that their children are learning the proper use of dentifrices, and once they are assured of this, supervision is no longer required. The agency agrees that the labeling should make this point without being unnecessarily overcautious or alarmist.

Regarding the request to expand § 355.50(d)(1) to include the language "To prevent swallowing * * *," the agency agrees that the objective of instruction and supervision is to avoid excessive ingestion of the dentifrice. However, the agency believes that the word "prevent" may be too strong a term and that prevention of some swallowing of dentifrices is unachievable in young children. The amount of dentifrice ingested varies with the age and skill of the child. The Panel reviewed a study (Ref. 1) involving children 2 to 6 years of age that showed large individual variations in expectorated volumes after mouthrinsing with water. Only a few of

the children between 2 and 3 years of age could perform mouthrinsing without swallowing the fluid. The 3- and 4-year-old children could, as a rule, keep the fluid in their mouths for 30 seconds. The 5- and 6-year-old children could all perform the rinse for 1 minute; these children had considerably less individual variation in expectorated volumes. Based on these data, the agency finds that suggesting to parents that swallowing can be prevented may cause unnecessary alarm when they observe a young child swallow small amounts of dentifrice during the learning process. Accordingly, the agency is using the word "minimize" instead of "prevent" in this final monograph. The revised direction statement in § 355.50(d)(1)(i) reads: "Instruct children under 6 years of age in good brushing and rinsing habits (to minimize swallowing). Supervise children as necessary until capable of using without supervision."

Reference

(1) Ericsson, Y., and B. Forsman, "Fluoride Retained from Mouthrinses and Dentifrices in Preschool Children," *Caries Research*, 3:290-299, 1969.

25. One comment objected to the part of the proposed directions in § 355.50(d)(2)(i) for anticaries products marketed for use as treatment rinses, which states: "Children under 12 years of age should be supervised in the use of this product." The comment stated that the Panel recommended that children under 6 years of age be supervised in the use of fluoride dentifrices (45 FR 20666 at 20673), but did not mention children above 6 years of age. The comment suggested that the Panel's recommendation was made in order to limit daily fluoride ingestion and thereby avoid possible dental fluorosis. The comment cited the Panel's discussion of epidemiological and clinical findings that indicated that teeth of children 6 years of age and older are "(excepting third molars) * * * too advanced to be affected by excessive daily fluoride ingestion." The comment mentioned the Panel's discussion (45 FR 20666 at 20673) that children 6 years of age and older have developed control of their swallowing reflexes and are able to rinse for 1 minute and expectorate properly. The comment stated that if the agency is concerned that children between 6 and 12 years of age using the product for the first time may not be able to follow label directions without instruction from a parent or other adult, then limited directions about supervision might be useful. However, the comment expressed concern that continuing

supervision each time the product is used did not appear warranted and that this unnecessarily overcautious labeling could discourage use of these products.

The agency agrees. As discussed in comment 24, the agency interpreted the Panel's statement to mean that children under 6 years of age should be properly instructed and supervised in the use of a dentifrice, not because of any particular hazard, but to ensure that the child is developing adequate toothbrushing skills and is using the product correctly. Instruction and supervision serve the same purpose for fluoride rinses (i.e., to assure proper use of these products) and are not intended to discourage use of fluoride rinses by children. Once the parent is certain that the child is using the product correctly, unsupervised use may be allowed. Therefore, the agency is revising part of the directions statement to read: "Instruct children under 12 years of age in good rinsing habits (to minimize swallowing). Supervise children as necessary until capable of using without supervision."

26. One comment disagreed with the agency's proposal to include the following statement in § 355.50(c) as a warning for concentrated treatment rinse solutions, powders, and effervescent tablets: "Do not use before mixing with water. Read the directions carefully." The comment stated that neither the Panel in the advance notice of proposed rulemaking (45 FR 20666) nor the agency in the tentative final monograph for OTC anticaries drug products identified a compelling safety hazard that warrants including the information in the warnings section rather than in the directions for use. The comment contended that the safe use of these concentrated products is amply ensured by including the quoted language in the directions for use. The comment requested that this information be included in the directions section only, because it concerns proper use of a product rather than cautioning to prevent possible dangers of misuse.

In the tentative final monograph, the agency stated that, 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 warning stated above for these dosage forms. The agency agrees with the comment that consumers could equally be alerted if this information appeared in the directions for use section. Accordingly, in this final monograph, the agency is moving the statement "Do not use before mixing with water." from the

warnings to the directions for use section. This statement is to appear as the first statement under the directions for use for concentrated treatment rinse solutions, powders, and effervescent tablets. It should then be followed by the proper directions for preparing the diluted rinse product. The part of the proposed warning that stated "Read the directions carefully." is not needed when this revised labeling format is used.

27. Several comments objected to the agency's proposed labeling statement in § 355.50(e)(3) for OTC stannous fluoride-containing dentifrices, treatment gels, and treatment rinses, which states: "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." In support of their objections to this statement, one comment cited five published studies (Refs. 1 through 5) and another comment submitted an unpublished study of the incidence of stained teeth in school children who used a stannous fluoride dentifrice (Ref. 6). Stating that the evidence regarding the propensity of stannous fluoride products to stain teeth is equivocal, another comment argued that the labeling statement should be required only on those stannous fluoride products that have been scientifically proven to cause substantial and discernible staining on the teeth of users. The comment urged the agency to abandon or strictly limit its proposal to require a teeth staining labeling statement on OTC stannous fluoride dentifrice products.

Three comments noted that the Panel specifically stated in its discussion of stannous fluoride dentifrice drug products (45 FR 20666 at 20685) 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 labeling statement on staining shall be required for stannous fluoride dentifrice formulations * * *." Two of the comments stated that the agency failed to offer any new evidence that would make the findings of the expert panel inappropriate. One of the comments asserted that all the studies cited by the agency in support of the proposed labeling statement for stannous fluoride dentifrice products (50 FR 39854 at 39865 and 39866) were cited previously by the Panel as support for its conclusion that no labeling statement about tooth staining was necessary (45 FR 20666 at 20685). Another comment mentioned extensive experience with the first stannous

fluoride dentifrice formulation marketed in the United States. This comment stated that no incidence of surface staining was found that would justify such a labeling statement.

One comment suggested that the tendency of stannous fluoride products to cause staining of the teeth is directly related to a number of factors. It may be highly dependent on the formulation of the product and/or the brushing habits of the user. The comment stated that the stability of the fluoride and the stannous ions in a product have an effect on whether or not the product causes tooth staining. For example, a product that contains a high level of stannous ions may be more likely to stain teeth than a product that is stabilized and, therefore, does not contain many stannous ions. The comment asserted that stable stannous fluoride products (e.g., dental gels) are not likely to cause discernible staining. The comment concluded that the labeling statement about tooth staining should not be imposed indiscriminately on all stannous fluoride products without regard to the stability of the product.

One comment contended that requiring the labeling statement about tooth staining on stannous fluoride dentifrice products would cause undue concern among consumers. The comment was concerned that the proposed warning would cause users to avoid safe and effective stannous fluoride products in favor of other products that do not bear such a warning. Another comment stated that requiring such a labeling statement without reliable scientific support is damaging to consumers who may place undue emphasis on the possibility of some transient staining. The first comment added that requiring the labeling statement regardless of whether or not a product caused staining of the teeth would handicap stannous fluoride products that could be shown not to cause a greater amount of staining than any other fluoride product.

Another comment contended that the data used by the agency to support the tooth staining labeling statement (50 FR 39854 at 39865 and 39866) are flawed and do not support the agency's decision to require this statement on stannous fluoride products. Stating that none of the studies attempted to relate the incidence of staining to any element of the dentifrice other than stannous fluoride, the comment asserted that interaction between the polishing agent (abrasive) and the fluoride moiety may be responsible for any staining observed. The comment noted that the polishing agent in the stannous fluoride dentifrices in some studies was sodium

metaphosphate. The comment maintained that it is impossible to know whether similar results would have occurred if a different polishing agent had been used. The comment concluded that these data show that stannous fluoride contained in a dentifrice base of sodium metaphosphate can cause mild staining in some subjects when analyzed by investigators in blind, controlled settings.

The comment added that the studies used by the agency to support the proposed staining statement (50 FR 39854 at 39865 and 39866) did not compare the reported incidence of tooth staining with consumer perception of such staining. The comment maintained that these studies demonstrate that tooth staining caused by stannous fluoride products is barely perceptible by consumers and is of little importance to the vast majority of people under normal conditions of daily use. The comment and another comment mentioned a study by Ness, Rosekrans, and Welford (Ref. 5) that also demonstrates that staining is barely perceptible and not important to consumers.

One comment agreed with the Panel that a labeling statement about tooth staining is unnecessary for stannous fluoride dentifrices. However, the comment asserted that, if the agency determines that such a labeling statement is necessary, the data support only a limited labeling statement for stannous fluoride dentifrice products in which sodium metaphosphate is the polishing agent. In addition, the comment requested that this labeling statement be modified to reflect the underlying data as follows: "This product may occasionally produce minor temporary surface staining of teeth. Adequate toothbrushing will prevent these stains and they may be easily removed by your dentist."

The agency does not believe that the studies submitted by the comments support eliminating the labeling statement regarding tooth staining from stannous fluoride dentifrice products. Although two of the six studies submitted do not show significant staining caused by stannous fluoride dentifrice products (Refs. 5 and 6), four of the six studies (Refs. 1 through 4) demonstrate that test groups using stannous fluoride dentifrice products had significantly more tooth staining than groups using dentifrice products without fluoride. Three of these studies (Refs. 1, 2, and 4) used a dentifrice with calcium pyrophosphate as the abrasive agent. Sodium metaphosphate was the abrasive agent used in the other study (Ref. 3). These studies do not indicate

that tooth staining is related to any individual polishing agent. However, based on the information available from the studies, the agency is unable to determine if staining is a formulation specific problem. The agency believes that the information submitted clearly demonstrates that stannous fluoride dental products (i.e., dentifrices, nses, and gels) have the potential to produce surface staining of the teeth. The agency is not aware that such staining results from the use of any other commonly utilized fluoride ingredients.

The agency reaffirms its conclusion that a labeling statement regarding tooth staining should be required on all stannous fluoride products. The agency believes that: (1) Consumers should be advised that staining of the teeth may be caused by stannous fluoride products, including dentifrices, and (2) that adequate brushing or dental prophylaxis may prevent the stains. The agency does not believe that one comment's suggested labeling statement about tooth staining has any advantage over the statement proposed by the agency in the tentative final monograph. The comment's suggested statement uses words like "occasionally" and "minor" and is more ambiguous than the agency's proposed statement. The agency's statement conveys a more meaningful message using the phrase "may produce surface staining." In addition, the agency's statement advises the consumer that the staining is not harmful or permanent. The agency considers its proposed statement to be more informative than the comment's suggested statement and more helpful to consumers. Therefore, the agency is including its proposed labeling statement in § 355.50(e)(2) of this final monograph.

References

- (1) Jackson, D., and P. Sutcliffe, "Clinical Testing of a Stannous Fluoride-Calcium Pyrophosphate Dentifrice in Yorkshire School Children," *British Dental Journal*, 123:40-48, 1967.
- (2) James, P. M. C., and R. J. Anderson, "Clinical Testing of a Stannous Fluoride-Calcium Pyrophosphate Dentifrice in Buckinghamshire School Children," *British Dental Journal*, 123:33-39, 1967.
- (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) Slack, G. L. et al., "Clinical Testing of a Stannous Fluoride-Calcium Pyrophosphate Dentifrice in Essex School Girls," *British Dental Journal*, 123:26-33, 1967.
- (5) Ness, L., D. L. Rosekrans, and J. F. Welford, "An Epidemiological Study of Factors Affecting Extrinsic Staining of Teeth in an English Population," *Community*

Dentistry and Oral Epidemiology, 5:55-60, 1977.

(6) Katayama, T., "Incidence of Stained Teeth on School Children Who Have Used Stabilized SnF₂ Toothpaste for Three Years," unpublished study in Comment No. C63, Docket No. 80N-0042, Dockets Management Branch.

28. One comment requested that the professional labeling in § 355.60 be modified to require that only dental rinse formulations composed of ingredients suitable for swallowing be used as fluoride supplements intended for ingestion in areas where the water supply is nonfluoridated. The comment stated that this section, as proposed, does not mention that fluoride rinses promoted to health professionals and not offered to the general public are specially formulated with ingredients suitable for ingestion. These products are intended to be swallowed. The comment mentioned that dental rinse products not intended to be swallowed are formulated differently and contain other ingredients.

The agency agrees that further explanation of the term "supplement" would help to reduce possible confusion. Therefore, the agency is modifying the introductory language in the professional labeling in § 355.60 as follows: "The labeling for anticaries fluoride treatment rinses identified in § 55.10 that are specially formulated so they may be swallowed (fluoride supplements) and are provided to health professionals (but not to the general public) may contain the following additional dosage information: * * *." Also, the agency is including a definition of fluoride supplement in § 355.3 as follows: "Fluoride supplement. A special treatment rinse dosage form that is intended to be swallowed, and is promoted to health professionals for use in areas where the water supply contains 0 to 0.7 parts per million fluoride ion."

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

29. One comment objected to the proposed prescription-to-OTC switch of 0.4 percent stannous fluoride gel products for economic and labeling reasons. The comment indicated that currently only small manufacturers make and market these products on a prescription basis. The comment asserted that OTC status would disadvantage these small companies by forcing them into the OTC marketplace with obvious competitive and marketing expenses. According to the comment, promoting its products through health-care professionals is less costly than promoting the products to the general

public on an OTC basis. The comment contended that OTC status creates a labeling problem that does not exist when these products are marketed as prescription drugs. The comment identified this problem as a "negative statement" required in the product's labeling, i.e., "not a toothpaste." The comment concluded by suggesting that the interests of the consuming public and "small" entities are best served by not including 0.4 percent stannous fluoride gel in the OTC drug monograph and by continuing its prescription status.

The agency does not agree with the comment. The Panel recommended that certain fluoride dental rinses and gels, which had previously been restricted to prescription use, be made available OTC provided that they conform to package size limitations and proper labeling to avoid misuse (45 FR 20666 at 20666, 20674, and 20691). (Package size limitations are discussed in section I.G., comment 46.) The Panel reviewed four published studies on stannous fluoride dental gels containing 0.4 percent stannous fluoride in an anhydrous glycerin gel (45 FR 20682) and concluded that these studies provide sufficient documentation of the safety and effectiveness of this dental gel dosage form for OTC use. In the tentative final monograph (50 FR 39854 at 39858), the agency concurred with the Panel's recommendation that 0.4 percent stannous fluoride in an anhydrous glycerin gel be switched to OTC status and labeled with proper directions for use (45 FR 20688).

The agency is aware that the change of 0.4 percent stannous fluoride dental gels from prescription-to-OTC status will lead to different marketing strategies and promotional activities. However, the agency has determined that such a product can be generally recognized as safe and effective and marketed as an OTC product. This OTC status does not prevent a manufacturer from continuing to promote the use of such products through health-care professionals, who then would instruct their patients to purchase and use the products.

In response to the comment's objection to the proposed labeling of its product with the statement "This is not a toothpaste," the agency indicated in the tentative final monograph (50 FR 39869) that a nonabrasive dental gel packaged in a conventional tube can be confused with a conventional abrasive-containing dentifrice. There is also a safety concern because dentifrices contain an abrasive, while these dental gels do not. This safety concern is discussed in section I.G., comment 46 of

this document. The agency considers the statement for dental gel products to be important to their safe OTC use.

The agency concludes that the OTC availability of 0.4 percent stannous fluoride dental gel products provides benefit to consumers and poses very little risk of misuse when the products are packaged and labeled properly. Therefore, the agency is including 0.4 percent stannous fluoride dental gel products in this final monograph.

30. One comment objected to the 120-mg package size limitation for fluoride treatment gels proposed in § 55.20. The comment requested that a 7-ounce (oz) package size for 0.4 percent stannous fluoride preventive treatment gels (containing 192 mg total fluoride) remain in the marketplace, at least as a prescription drug product for use under the supervision and direction of the dental profession. The comment noted that its decision to market a 7-oz package size of 0.4 percent stannous fluoride treatment gel was partially based on the 7-oz package size of 0.4 percent stannous fluoride dentifrice products marketed at the time its product was introduced into the marketplace. The comment noted that, in the tentative final monograph (50 FR 39854 at 39857), the agency cited the position and experience since 1958 of the ADA concerning package size limitations for OTC rinses and gels in support of the proposal in § 355.20 to limit package sizes for dental rinses and gels.

The comment mentioned over 10 years of safe prescription marketing of its 7-oz product with a child-proof safety closure. The comment contended that consumer use is different with regard to the safe handling of prescription drug products, as compared to OTC drug products. The comment noted that the agency concluded in the tentative final monograph that a toxic dose of fluoride via a dentifrice drug product could not be ingested without vomiting, although the agency did not address the effect of glycerin (which is used in the treatment gel) with regard to vomiting. The comment stated that the 7-oz package size of this product represents over 50 percent of its dollar volume and its discontinuance would represent a hardship. The comment requested reconsideration of the OTC status of the 7-oz package size for its 0.4-percent stannous fluoride treatment gel. The comment stated that, at a minimum, allowing this product to remain in the marketplace on a prescription basis would best serve the interests of the dental profession and small businesses in the stannous

fluoride industry without endangering public safety.

In the tentative final monograph (50 FR 39854 at 39857), the agency concurred with the Panel's recommendation that the package size of OTC preventive treatment gel products be limited to 120 mg total fluoride because of possible safety concerns. The Panel was concerned about the significant differences in the amount of fluoride available for pharmacological or toxicological action between dentifrices (abrasive-containing) and nonabrasive treatment gels and rinses. Available fluoride in a dentifrice is dependent upon the chemical reactivity of the fluoride ion with the abrasive (45 FR 20675 to 20677), while all of the fluoride ion in the nonabrasive preventive treatment gel is available. There are potential safety concerns (i.e., ingestion of an entire package that could cause serious effects, particularly for a small child) when the 120-mg total fluoride package size limitation for a preventive treatment gel is exceeded. This package size limitation appears in § 355.20 of this final monograph. Although the package size will vary depending on the concentration of the fluoride ingredient in the product, the maximum OTC package size of a 0.4-percent stannous fluoride preventive treatment gel product is 4.375 oz. The agency has no objection to larger size packages being available as prescription drug products. However, if a manufacturer wishes to market a 0.4-percent stannous fluoride preventive treatment gel product in a larger package size on a prescription basis, the manufacturer must obtain an approved NDA under section 505 of the act (21 U.S.C. 355) and part 314 of the regulations.

The comment provided no data or information in support of its contention that the general public handles prescription drugs differently than OTC drugs. The agency believes that more potent prescription drug products generally are handled differently than most OTC drugs. However, the agency is unaware of any data that suggest that consumers handle prescription anticaries gels and treatment rinses differently than OTC anticaries fluoride mouthwashes and rinses.

The agency indicated in the tentative final monograph (50 FR 39857) that the safety of dentifrice pastes containing up to 260 mg fluoride can be attributed to: (1) The decreased amount of fluoride actually available for absorption because of the reactivity of fluoride with the abrasive in dentifrice pastes; and (2) the likelihood that the amount of dentifrice that contains a toxic dose of fluoride

could not be ingested without vomiting. The comment provided no information or data on the effect of glycerin in a dental gel with regard to vomiting in support of its contention that larger package sizes be allowed for the gel dosage form. Without data, the agency cannot determine glycerin's role on vomiting if large amounts of a dental gel were to be ingested. In conclusion, the agency does not consider the comment's arguments supportive of its requests that 0.4 percent stannous fluoride gels remain prescription drugs or that the 120-mg package size be increased for such products marketed on an OTC basis.

E. Comments on Combination Anticaries Drug Products

31. One comment submitted new data and information to support the safety and effectiveness of a combination drug product containing 0.05 percent sodium fluoride and 1.5 percent hydrogen peroxide. The comment stated that this combination drug product, which was not considered in the tentative final monograph for OTC anticaries drug products, is targeted for once-daily use in an orthodontic population. The comment contended that this combination of ingredients provides rational, concurrent therapy as an oral cleanser and anticaries agent for orthodontic patients for two reasons: (1) Orthodontic appliances occasionally cause minor irritation or injury to the oral mucosa and the product cleanses these irritations or injuries, and (2) the configuration of the orthodontic appliance and its duration of use may cause decalcification of teeth in orthodontic patients and the product reduces tooth decalcification.

The comment stated that the safety of the 0.05-percent sodium fluoride component of the product was recognized by FDA in the tentative final monograph for OTC anticaries drug products (50 FR 39854 at 39872). The comment submitted data (Ref. 1) from an enamel solubility reduction test and an enamel fluoride uptake test to support the effectiveness of the sodium fluoride in the combination product. The comment also submitted a clinical study of the combination product to support the safety of daily exposure of the oral mucosa to 1.5 percent hydrogen peroxide for an 18-month period (Ref. 1). The comment added that the effectiveness of up to 3 percent hydrogen peroxide as an oral cleanser was established in the tentative final monograph for OTC oral health care drug products published in the *Federal Register* of January 27, 1988 (53 FR 2436). Based on these data, the

comment requested that the agency include this combination product in the final monograph for OTC anticaries drug products.

The agency agrees that 0.05 percent sodium fluoride and 1.5 percent hydrogen peroxide may be a rational combination for concurrent therapy in orthodontic patients. However, as the agency discussed in the tentative final monograph for OTC oral health care drug products, the Advisory Review Panel on OTC Oral Health Care Drug Products (Oral Cavity Panel) was concerned about the chronic use of hydrogen peroxide in products such as antimicrobial mouthwashes (53 FR 2436 at 2446 and 2447). The agency further stated in this discussion that the effects of long-term OTC use of hydrogen peroxide would be considered as part of the antiseptic segment of the oral health care drug products rulemaking.

After that tentative final monograph was published, the agency published a call-for-data for OTC antiplaque drug products in the *Federal Register* of September 19, 1990 (55 FR 38560). The data submitted to the agency as a result of this call-for-data will be evaluated by the Dental Products Panel. That Panel will consider, among other things, the safety of the long-term oral use of hydrogen peroxide solutions. The agency believes that the Dental Products Panel is the appropriate forum to consider whether a combination product containing 0.05 percent sodium fluoride and 1.5 percent hydrogen peroxide can be generally recognized as safe and effective for long-term OTC use in the oral cavity. The agency has informed the manufacturer that it considers the combination product to be a new drug that may not be introduced or delivered for introduction into interstate commerce without an approved NDA (Ref. 2). The agency has deferred this product to the Dental Products Panel and will address the submitted data as part of the OTC oral health care rulemaking applicable to antiplaque drug products.

References

- (1) Comment No. C80, Docket No. 80N-0042, Dockets Management Branch.
- (2) Letter from R. J. Chastonay, FDA, to R. Finn, Chesebrough-Pond's USA Co., in OTC Vol. 08AFM, Docket No. 80N-0042, Dockets Management Branch.

32. Two comments requested the agency to include the combination of sodium fluoride with sodium monofluorophosphate in a dentifrice in the final monograph. The comments contended that the combination of two Category I fluoride ingredients, particularly sodium fluoride and

sodium monofluorophosphate, provides a rational combination that has an enhanced therapeutic effect and satisfies the agency's combination policy in § 30.10(a)(4)(iv) (21 CFR 330.10(a)(4)(iv)).

One comment submitted two clinical studies (Refs. 1 and 2) to support the combination of two fluoride ingredients in a dentifrice. The first study (Ref. 1) was a 3-year double-blind, randomized clinical study involving 799 children 14 to 15 years old. Two combination dentifrices, each containing 0.76 percent sodium monofluorophosphate (1,000 ppm theoretical total fluorine) and 0.10 percent sodium fluoride (455 ppm theoretical total fluorine) (to provide a theoretical total fluorine level of 1,455 ppm) were compared with a fluoride-free control dentifrice and with a positive control 0.76 percent sodium monofluorophosphate dentifrice (1,000 ppm theoretical total fluorine). One of the two experimental combination fluoride dentifrices had an alumina abrasive system. The other had a dicalcium phosphate abrasive system. The combination dentifrices reduced the incidence of dental caries by approximately 26 percent compared with the fluoride-free placebo dentifrice, and by approximately 15 percent compared with the positive control 0.76 percent sodium monofluorophosphate dentifrice with an alumina abrasive system.

The second study (Ref. 2) was a 3-year clinical trial that involved school children who resided in an area with nonfluoridated water. Two combination dentifrices containing sodium monofluorophosphate and sodium fluoride, either 1,450 or 2,000 ppm theoretical total fluorine, were compared to a sodium monofluorophosphate dentifrice containing 1,000 ppm theoretical total fluorine. Results indicated that after 3 years of unsupervised brushing, the children who used either the 1,450- or 2,000-ppm fluoride dentifrice combinations developed fewer cavities than those who brushed with the 1,000-ppm sodium monofluorophosphate dentifrice. No significant difference in caries reduction between the 1,450-ppm and 2,000-ppm fluoride dentifrices was reported.

Another comment submitted laboratory and clinical data (Ref. 3) to support the safety and effectiveness of a dentifrice containing sodium fluoride (1,000 ppm) and sodium monofluorophosphate (420 ppm). In one study, enamel specimens exposed for 24 hours to a suspension of sodium monofluorophosphate alone or in combination with sodium fluoride had

greater fluoride uptake with the combination fluorides than with sodium monofluorophosphate alone. In another study, a nearly three-fold reduction in enamel solubility was shown with the combination of sodium fluoride and sodium monofluorophosphate compared to sodium monofluorophosphate alone. The comment also provided a graph of enamel solubility reduction data from dentifrices containing sodium fluoride or sodium monofluorophosphate alone or various combinations of sodium monofluorophosphate and sodium fluoride. The comment noted that a combination containing 75 percent sodium fluoride and 25 percent sodium monofluorophosphate would be optimal. The comment contended that this combination produces twice as much reduction in enamel solubility as either of the ingredients alone at comparable fluoride concentrations.

The comment included an animal study in which male rat pups were inoculated with streptococci (strain not provided) and placed on a standard cariogenic diet for 3 weeks. During this period, the teeth were brushed with a sodium monofluorophosphate/sodium fluoride dentifrice combination or a control fluoride dentifrice (active ingredient and strength not specified). The results of this study indicated that the combination of sodium fluoride and sodium monofluorophosphate was significantly more "cariostatic" than the single fluoride dentifrice.

The comment also mentioned a 3-year clinical study involving 573 school children. This study was designed to determine the anticaries effect of a dentifrice containing a sodium monofluorophosphate/sodium fluoride combination (1,420 ppm) with a comparable control toothpaste containing only sodium monofluorophosphate (1,315 ppm). After 2 and 3 years of unsupervised brushing, the number of new decayed, missing, or filled (DMF) surfaces was 12 to 50 percent lower in the combination fluoride group than in the sodium monofluorophosphate control group. Based on the results of this study, the comment concluded that the combination of sodium fluoride and sodium monofluorophosphate is significantly more effective than sodium monofluorophosphate alone in reducing the incidence of dental cavities.

The comment acknowledged that combinations of fluoride active ingredients have not been marketed in the United States. The comment stated, however, that the combination of sodium fluoride and sodium monofluorophosphate has been widely

available in the United States for many years. The comment stated that this combination occurs as a result of the hydrolysis of sodium monofluorophosphate during contact with the tooth surface and during the aging process of the fluoride dentifrice formulation itself. The comment indicated that as the dentifrice ages, sodium monofluorophosphate undergoes hydrolysis resulting in a significant increase of sodium fluoride within the sodium monofluorophosphate formulation. The comment added that in the oral environment sodium fluoride may represent more than 50 percent of the hydrolyzed fluoride species in contact with the tooth surface as a result of the hydrolysis of sodium monofluorophosphate alone. The comment included several studies showing that sodium monofluorophosphate undergoes rapid hydrolysis in saliva and even more rapid hydrolysis in the presence of plaque microorganisms. In one study (Ref. 3), during a short period of toothbrushing, the levels of fluoride ions in saliva were initially much lower with the sodium monofluorophosphate dentifrice than with the comparable sodium fluoride preparation. However, after 10 minutes in saliva, both dentifrice formulations provided almost similar levels of fluoride ions. The comment stated that the uncontrolled hydrolysis of the two fluoride agents results in an important, but suboptimal, increase in the bioavailability of fluoride ions. The comment indicated that a combination of fluoride ingredients may provide greater product stability if the agency allows manufacturers the opportunity to control the ratio of these two fluoride ingredients in the dentifrice formulation. According to the comment, this would be better than relying on the unpredictable chemical process of hydrolysis to create a fluoride combination product. The comment asserted that its dentifrice product controls the process of hydrolysis by providing a combination fluoride dentifrice with a fluoride ingredient ratio of 3 to 1 (sodium fluoride to sodium monofluorophosphate), thereby enhancing the therapeutic effect of the anticaries product. However, the comment did not indicate how it proposed to control the hydrolysis of the one-quarter proportion of sodium monofluorophosphate in its product. This information is particularly significant if the hydrolysis of sodium monofluorophosphate occurs as rapidly in the mouth as the comment indicated.

The comment maintained that the fluoride ion is the effective anticaries moiety, and it is irrelevant whether the fluoride ion comes from one fluoride salt or a combination of two fluoride salts, as long as the fluoride ion is present in safe and effective quantities. The comment concluded that these data demonstrate the safety and effectiveness of the combination of sodium fluoride and sodium monofluorophosphate in a dentifrice product. The comment urged the agency to include the combination of sodium fluoride with sodium monofluorophosphate in a 3 to 1 ratio as a dentifrice in the final monograph.

The agency has reviewed the available data and concludes that they do not support the comments' claims. The data do not demonstrate the cariostatic superiority of combination dentifrices containing sodium fluoride and sodium monofluorophosphate compared to conventionally formulated 0.76 percent sodium monofluorophosphate dentifrices. The data do not show that the effect of the sodium fluoride/sodium monofluorophosphate combination is greater than the effect achieved by the individual active ingredients alone at comparable fluoride ion concentrations.

A combination drug product containing Category I active ingredients from the same therapeutic category must satisfy the criteria in § 330.10(a)(4)(iv). The "General Guidelines for OTC Drug Combination Products, September 1978" give clarifying examples regarding the combination policy (Ref. 4). Paragraph 3 of these guidelines states:

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

The agency has not received sufficient data to conclude that the use of a combination fluoride product has an advantage over or is more effective in controlling the incidence of dental caries than a product containing a single fluoride active ingredient at comparable fluoride ion concentrations.

In the clinical studies submitted by the comment, there was no comparison of a combination and single ingredient product at comparable fluoride concentrations. The agency notes that

the higher levels of fluoride concentration in the combination dentifrices, 1,455 ppm (Ref. 1) and 1,450 or 2,000 ppm (Ref. 2), as compared to the fluoride levels in the positive control single fluoride ingredient dentifrice (1,000 ppm), most likely account for the enhanced effectiveness of the combination products. Because of these higher concentrations, the presence of two sources of fluoride ions may be unrelated to the observed increase in effectiveness.

The agency has also evaluated two other clinical studies (Refs. 6 and 7) that compared comparable fluoride concentrations (1,000 ppm) for a single-ingredient sodium monofluorophosphate dentifrice and a combination containing sodium fluoride and sodium monofluorophosphate. In these studies, the two dentifrices were comparably effective. One study (Ref. 6) was a 31-month, double-blind clinical study involving 1,027 school-aged children. The anticaries effectiveness of a single fluoride ingredient dentifrice containing sodium monofluorophosphate (1,000 ppm theoretical total fluorine) was compared with a combination fluoride dentifrice containing sodium fluoride and sodium monofluorophosphate (1,000 ppm theoretical total fluorine, with 500 ppm contributed by each fluoride ingredient). During this study, the children brushed daily in school under supervision and were clinically and radiologically examined annually. After 31 months of use, no statistically significant difference in the incidence of dental caries was observed between children in the two dentifrice groups.

In the second study (Ref. 7), the effectiveness of three dentifrices was compared over a 2-year period. The study involved 2,769 children; a nearly equal number did unsupervised brushing at home with one of the following dentifrices: (1) Sodium monofluorophosphate (1,000 ppm), (2) a combination of sodium fluoride and sodium monofluorophosphate containing equimolar amounts of each active ingredient (theoretical total fluorine of 1,000 ppm), or (3) a combination of sodium fluoride and sodium monofluorophosphate containing equimolar amounts of each active ingredient (theoretical total fluorine of 2,500 ppm). The results of this study indicated no significant differences in caries inhibition among the dentifrices tested.

In most of the *in vitro* studies submitted (Ref. 3), exposure times of the tooth enamel surface to suspensions of dentifrice were for lengthy periods of time ranging from 30 minutes to 24

hours. The agency questions the relevancy of a 24-hour exposure time when the exposure time to a dentifrice formulation in the mouth during actual toothbrushing is a few minutes only. In the animal study measuring the effect of three dentifrices on the incidence of caries in rats, no details were given regarding the active ingredients or the fluoride concentrations in the dentifrices tested. Regarding hydrolysis during the aging process of sodium monofluorophosphate products, the Panel stated that sodium monofluorophosphate exists in water in dynamic equilibrium with sodium fluoride, and with the various ions produced by the hydrolysis of the compound (45 FR 20666 at 20674). The agency does not consider this reaction as producing a combination drug product. The agency considers the sodium monofluorophosphate compound as a single active ingredient, even though it is aware that the compound always contains some amounts of sodium fluoride.

In conclusion, the agency has determined that the submitted information and data do not demonstrate the cariostatic superiority of combination dentifrices containing sodium fluoride and sodium monofluorophosphate relative to single-ingredient fluoride dentifrices with a comparable fluoride ion concentration. Accordingly, these fluoride combinations are not included in this final monograph.

References

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- (2) Diodati, R. R. et al., "Clinical Anticaries Effect of Various Fluoride Dentifrices," Abstract No. 258, *Journal of Dental Research*, 65:198, 1986.
- (3) Comment No. C00059, Docket No. 80N-0042, Dockets Management Branch.
- (4) Food and Drug Administration "General Guidelines for OTC Drug Combination Products, September 1978," Docket No. 78D-0322, Dockets Management Branch.
- (5) Conti, A. J. et al., "A 3-Year Clinical Trial to Compare Efficacy of Dentifrices Containing 1.14 Percent and 0.76 Percent Sodium Monofluorophosphate," *Community Dental Oral Epidemiology*, 16:135-138, 1988.
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- (7) Ripa, L. W. et al., "Clinical Comparison of the Caries Inhibition of Two Mixed NaF-Na₂PO₃F Dentifrices Containing 1,000 and 2,500 ppm F Compared to a Conventional Na₂PO₃F Dentifrice Containing 1,000 ppm F:

Results after Two Years," *Caries Research*, 21:149-157, 1987.

F. Comments on Testing Guidelines

33. One comment agreed with the agency's conclusion that laboratory test data are not adequate to establish comparative claims of effectiveness for anticaries active ingredients (53 FR 22430 at 22446). However, the comment contended that the agency should recognize the possibility that, in certain cases, claims of superior performance in a laboratory test may be desirable. As a hypothetical example, the comment stated that it may be important to a dental professional that (1) one active ingredient provides more rapid fluoride uptake than another and (2) this performance could promote hardening of enamel in certain instances. The comment suggested that such claims could be made in professional labeling without needing clinical studies for support.

The agency reiterates its conclusion that the extension of laboratory test data to a comparative evaluation of effectiveness between different fluoride products or fluoride active ingredients is inappropriate (53 FR 22446). In general, the agency does not believe that claims of superior performance in a laboratory test are appropriate for use in either the consumer or professional labeling of OTC anticaries drug products unless that superior performance has been shown to have clinical significance. However, the agency will evaluate any such laboratory test data submitted on a case-by-case basis.

34. One comment (from an agency dental reviewing officer) objected to the use of Laboratory Testing Profiles (LTP's) for final formulation testing for Category I active ingredients in fluoride dentifrice formulations. The comment expressed unawareness of any data submitted to the agency demonstrating that the results from the biological test requirements in the LTP's were correlated with adequate and well-controlled anticaries clinical studies. The comment did not submit any data demonstrating that the LTP's do not correlate with clinical studies.

Two comments (from manufacturers) concurred with the agency's proposal that the LTP's be used to ensure the effectiveness of abrasive-containing fluoride drug products. One of the comments contended that, based on the current state of dental research, it is not necessary to do clinical studies to verify anticaries performance except in certain situations, such as the introduction of a new anticaries active ingredient.

Regarding the comment questioning whether the LTP's were correlated with

adequate and well-controlled clinical testing, the agency notes that the Panel based its recommendations on the results of actual biological tests performed on fluoride dentifrices that had been shown to be clinically effective in preventing caries (45 FR 20666 at 20677). Thus, the Panel's recommendations were based on the correlation of laboratory testing results with clinical results.

The agency considers the LTP final formulation test requirements in this final monograph to be adequate to ensure the safety and effectiveness of dentifrices containing fluoride active ingredients included in the monograph. In the tentative final monograph (53 FR 22430 at 22433), the agency stated reasons why it concurred with the Panel's recommended laboratory testing requirements, as set forth in the Panel's LTP tables (45 FR 20666 at 20679 to 20681) for Category I fluoride ingredient/abrasive combinations. Thus, the agency concludes that lengthy clinical trials are not necessary to ensure the safety and effectiveness of dentifrices containing monograph fluoride ingredients.

35. One company asked whether the monograph would preclude FDA's accepting valid clinical trials in lieu of LTP's. The comment noted the agency's statement in the tentative final monograph that the use of LTP's to establish efficacy should not in any way preclude the option of clinical testing as a final demonstration of efficacy for those companies that prefer to use this method (53 FR 22430 at 22434).

The monograph does not preclude manufacturers from performing clinical testing to ensure the effectiveness of a fluoride dentifrice. However, the regulatory requirement for all fluoride dentifrice drug products marketed

pursuant to the monograph is that the product must meet the final formulation test requirements (LTP's) included in § 355.70.

36. One comment stated that all toothpaste advertised as containing fluoride should be tested for stannous fluoride concentration, per unit volume or weight. The comment contended that this is necessary to ensure that the concentration of stannous fluoride is not being reduced.

There are a number of requirements applicable to fluoride dentifrices that will ensure the fluoride concentration of the product. While toothpastes can contain one of several different fluoride ingredients, the LTP's included in the final monograph are intended to ensure available fluoride ion in the final products. The aged minimal fluoride ion values in the LTP tables are used to determine the product's expiration date. This date provides consumers relevant information regarding use of the product. In addition, § 211.166 of the agency's current good manufacturing practice regulations (21 CFR 211.166) contains stability testing requirements for drug products, including toothpastes. Accordingly, these requirements address the comment's concern.

37. Two comments requested that the agency revise LTP Table 3 to include corrected test values submitted by the industry for stannous fluoride dentifrices (45 FR 20666 at 20681). One comment noted that the agency's revisions in the LTP tables discussed in the tentative final monograph (53 FR 22430 at 22435 and 22436) omitted a correction mentioned in an earlier comment concerning stannous fluoride that was made to this rulemaking. The comment requested that the agency revise Table 3 under "II. Soluble

Stannous Ion." by inserting a statement indicating that the test dilution for the silica abrasive should remain 1:10 as stated in the tentative final monograph (45 FR 20666 at 20681). The second comment indicated that the appropriate values for soluble fluoride should discriminate between dentifrices using insoluble sodium metaphosphate and silica abrasives. The comment indicated that in Table 3 for stannous fluoride dentifrices (45 FR 20681) under "I. Soluble Fluoride Ion," the test values for fluoride ion listed for the silica abrasive formulation should be 600 ppm for the fresh value and 500 ppm for the aged minimal value with a test dilution of 1:10, rather than 700 ppm for the fresh value and 650 ppm for the aged minimal value. The comment stated that this revision would discriminate between dentifrices using insoluble sodium metaphosphate and those using silica abrasives.

The agency recognizes that the data the Panel used to establish the LTP tables were developed by industry and submitted to the Panel to provide a basis for the LTP tables. The agency has reviewed the industry's corrections of the LTP tables as noted above and agrees that these corrections should be made. However, the agency does not find it necessary to insert an additional clarification statement in the corrected LTP tables as requested by one comment. Instead, the agency has revised the LTP tables to reflect the changes made to the tables in the tentative final monograph (53 FR 22435 and 22436) and in this final monograph (see section I.B., comments 10, 13, 14, and 15 of this document, and section I.F., comments 38, 39, and 42 of this document) as follows:

TABLE 1.—ACCEPTABLE TEST VALUES FOR 1,000 PPM THEORETICAL TOTAL FLUORINE SODIUM FLUORIDE DENTIFRICES IN A PASTE DOSAGE FORM

I. Soluble Fluoride Ion (F⁻)

Abrasive	Fresh F ⁻ value ¹	Aged minimal F ⁻ value ^{1,2}	Test dilution (w/w)
High-beta-phase calcium pyrophosphate	648 ppm	403 ppm	1:3

II. Hydrogen Ion Concentration (pH)

Abrasive	Test value	Test dilution (w/w)
High-beta-phase calcium pyrophosphate	6.5 to 8.0	1:3

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

² Values listed are intended for use in determining expiration dating for fluoride dentifrices covered by the final monograph. These values are not intended to be used to determine if a dentifrice meets monograph requirements, i.e., is safe and effective.

TABLE 2.—ACCEPTABLE TEST VALUES FOR 1,000 PPM THEORETICAL TOTAL FLUORINE SODIUM MONOFLUOROPHOSPHATE DENTIFRICES IN A PASTE DOSAGE FORM
I. Soluble Fluoride Ions (PO_3F^- and F^-)¹

Abrasive	Ion	Fresh value ²	Aged minimal value ^{2,3}	Test dilution (w/w)
Applicable to all abrasives	PO_3F^-	650 ppm ⁴	Half total (PO_3F^- and F^-) value	1:10
	F^-	10 to 150 ppm	10 ppm to PO_3F^- value	1:10
	Total (PO_3F^- and F^-)	800 ppm	600 ppm	1:10

II. Hydrogen Ion Concentration (pH)

Abrasive	Test value	Test dilution (w/w)
Alumina	6.4 to 9.0	1:10
Calcium carbonate	7.0 to 10.0	1:10
Calcium pyrophosphate	5.0 to 5.4	1:10
Dicalcium phosphate	6.3 to 7.6	1:10
Insoluble sodium metaphosphate	5.6 to 6.9	1:10
Silica	5.5 to 7.4	1:10

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

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

³ Values listed are intended for use in determining expiration dating for fluoride dentifrices covered by the final monograph. These values are not intended to be used to determine if a dentifrice meets monograph requirements, i.e., is safe and effective.

⁴ Soluble PO_3 is derived either by direct analytical measurement or by subtracting soluble fluoride ion (F^-) from total soluble available fluoride (PO_3F^- plus F^-).

TABLE 3.—ACCEPTABLE TEST VALUES FOR 1,000 PPM THEORETICAL TOTAL FLUORINE STANNOUS FLUORIDE DENTIFRICES IN A PASTE DOSAGE FORM
I. Soluble Fluoride Ion (F^-)

Abrasive	Fresh F^- value ¹	Aged minimal F^- value ^{1,2}	Test dilution (w/w)
Insoluble sodium metaphosphate	700 ppm	650 ppm	1:3
Silica	600 ppm	500 ppm	1:10
Calcium pyrophosphate	288 ppm	108 ppm ³	1:3

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

Abrasive	Fresh Sn^{++} value ¹	Aged minimal Sn^{++} value ^{1,2}	Test dilution (w/w)
Insoluble sodium metaphosphate	2,000 ppm	Qualitatively detectable	1:10
Silica	Qualitatively detectable	Qualitatively detectable	1:10
Calcium pyrophosphate	900 ppm	Qualitatively detectable	1:3

III. Hydrogen Ion Concentration (pH)

Abrasive	Test value	Test dilution (w/w)
Insoluble sodium metaphosphate	4.2 to 5.4	1:4
Silica	4.6 to 5.1	1:4
Calcium pyrophosphate	4.4 to 5.1	1:3

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

² Values listed are intended for use in determining expiration dating for fluoride dentifrices covered by the final monograph. These values are not intended to be used to determine if a dentifrice meets monograph requirements, i.e., is safe and effective.

³ Value corresponds to that of aged product found clinically effective.

TABLE 4.—ACCEPTABLE TEST VALUES FOR ALL OTC FLUORIDE DENTIFRICES IN A PASTE DOSAGE FORM

I. Theoretical Total Fluorine¹

TABLE 4.—ACCEPTABLE TEST VALUES FOR ALL OTC FLUORIDE DENTIFRICES IN A PASTE DOSAGE FORM—Continued

- A. 850 to 1,150 ppm for all active ingredients
 B. 1,500 ppm for sodium monofluorophosphate

 II. Available Fluoride Ion Concentration¹

<i>Active Ingredient</i>	<i>Minimum Available Fluoride Ion¹</i>
<i>A. For 850 to 1,150 ppm Dentifrices:</i>	
Sodium fluoride	≥ 650 ppm
Sodium monofluorophosphate	≥ 800 ppm (consisting of PO ₃ F ⁻ and F ⁻ combined)
Stannous fluoride/calcium pyrophosphate	≥ 290 ppm
Stannous fluoride/with abrasive other than calcium pyrophosphate	≥ 700 ppm
<i>B. For 1,500 ppm Dentifrices:</i>	
Sodium Monofluorophosphate	≥ 1,275 ppm (consisting of PO ₃ F ⁻ and F ⁻ combined)

 III. Total Fluorine in Milligram Per Milliliter Dentifrice

- A. For 850 to 1,150 ppm Dentifrices:*
 0.935 to 1.955
B. For 1,500 ppm Sodium Monofluorophosphate Dentifrices:
 1.650 to 2.550

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

TABLE 5.—ACCEPTABLE TEST VALUES FOR SODIUM FLUORIDE/SODIUM BICARBONATE POWDERED DENTIFRICES CONTAINING 1,000 PPM THEORETICAL TOTAL FLUORINE

- I. Theoretical Total Fluorine¹
 850 to 1,150 ppm
 II. Minimum Available Fluoride Ion¹
 850 ppm
 III. Poured-bulk Density Range in Gram Per Milliliter Dentifrice
 1.0 to 1.2

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

TABLE 6—BIOLOGICAL TESTING REQUIREMENTS FOR ALL DENTIFRICES IN PASTE AND POWDER DOSAGE FORMS

- I. Animal Caries Reduction
 and,
 II. One of the Following Tests:
 A. Enamel Solubility Reduction
 B. Fluoride Enamel Uptake

38. One comment concurred with the agency's statement (53 FR 22430 at 22435) that measurements such as specific gravity, pH, stannous ion content, maximum test dilution, and lower limit of available fluoride at the expiration date should not be included in the final monograph. The comment agreed that these measurements are adequately addressed in the current good manufacturing practices (CGMP) regulations. The comment stated that the CGMP regulations in part 211 (21 CFR part 211) provide for acceptable outcomes of the performing, validating, recording, and reporting of procedures

in drug manufacturing, but the CGMP regulations do not provide test methods or acceptable values of measurement.

The comment provided the following example: If control of pH is important in manufacturing a dentifrice, the CGMP regulations provide that it is necessary to institute and document procedures for ensuring accurate recording, control of pH during the process, and acceptable checking of equipment. However, the comment stated that the regulations do not specify equipment, measurements, or the proper pH range. The comment contended that one could reasonably conclude that omission of

pH, specific gravity, stannous ion concentration, or maximum test dilutions from the provisions of the monograph means that manufacturers may set these specifications as they see fit.

However, the comment added that there are other statements in the agency's discussion of LTP's that cast doubt on the above interpretation. As an example, the comment cited the phrase "the allowable range for specific gravity (1.1 to 1.7) and theoretical total fluoride (850 to 1,150 ppm) * * *" (53 FR 22430 at 22437). The comment noted that, even though these ranges are given

equal force in this discussion, theoretical total fluoride is specified in proposed § 355, while specific gravity is not. The comment also mentioned the Panel's recommendations regarding specific pH guidelines (53 FR 22443) and the agency's statement that " * * * manufacturers should use the aged minimal fluoride ion limits provided in the LTP Tables * * * to determine the expiration dates for fluoride dentifrices * * *" (53 FR 22445). The comment added that the third agency change in the Panel's recommendations states that the agency is proposing the LTP values of pH and specific gravity (but not stannous ion levels, maximum test dilutions, or aged minimal fluoride levels) as guidelines of appropriate testing limits. The comment requested that the agency clarify its position on these matters.

The agency's proposal (53 FR 22430 at 22434 and 22435) states that fluoride dentifrices shall: (1) Meet or exceed the soluble fluoride ion level specified for each particular fluoride ingredient listed in the monograph, and (2) meet the requirements for biological testing. The agency included these criteria in the proposed monograph. Furthermore, the agency is including requirements pertaining to available fluoride content and biological testing in this final monograph. (See section I.F., comment 40 of this document.) These requirements must be satisfied for an anticaries dentifrice to be considered generally recognized as safe and effective.

The agency stated in the tentative final monograph (53 FR 22430 at 22435) that certain recommended requirements in the LTP tables are adequately addressed in the CGMP regulations (21 CFR part 211) and need not be specifically addressed in the monograph. These included parameters such as specific gravity and pH, which relate to inactive ingredients and appropriate manufacturing procedures. The CGMP regulations require establishing and following test methods and specifications that are appropriate and scientifically sound. These required methods and specifications may be found in a variety of sources (e.g., the United States Pharmacopeia/National Formulary or codified monographs).

The discussion about testing parameters not specifically included in the monograph (such as pH, specific gravity (w/v), stannous ion concentration, aged minimal fluoride ion values, and test dilution) was intended as guidance only. While these parameters are important to the manufacturer's product, only those requirements specifically set out in the

final monograph are considered essential by the agency and must be met. In the preamble to the tentative final monograph (53 FR 22435 and 22436), the agency revised the Panel's recommended testing guidelines for a number of testing parameters. The agency intended that these testing values be used solely as guidance for fulfilling CGMP requirements.

In this document, the agency has further revised the proposed testing guidelines for parameters other than available fluoride ion and biological test requirements (see section I.F., comments 35 and 39 of this document). These revised parameters are also intended only as guidance, e.g., for use in determining expiration dating. The agency is including a revised LTP chart in the preamble of this document for informational purposes (see section I.F., comment 37 of this document).

39. One comment stated its approval of the agency's proposed modification of the Panel's recommended ranges for theoretical total fluorine. The proposal set out a range of 0.935 to 1.955 mg theoretical total fluorine per mL for dentifrices with a specific gravity lower than 1.1 or higher than 1.7 (53 FR 22430 at 22438). The comment indicated that the proposed modification reflects the dynamic nature of dental research and provides innovation without compromising the required amount of fluoride ion available to the teeth with each brushing. The comment added that this single required range of theoretical total fluorine values more accurately defines the amount of fluoride ions available to the teeth during each brushing. For that reason, the proposed range is more descriptive of products that have been proven clinically effective. The comment suggested that a single theoretical total fluorine range would be better than the two previous proposed ranges of specific gravity and theoretical total fluorine. The comment contended that a single range would ensure consumers that the active ingredient in dentifrice products delivers the required concentration of fluoride ion, thus providing the desired anticaries effect.

In the tentative final monograph for OTC anticaries drug products (53 FR 22430 at 22437), the agency proposed a range of 850 to 1,150 ppm for theoretical total fluorine and a specific gravity range of 1.1 to 1.7. This range of values was intended to accommodate the newer, less dense abrasive systems without compromising the effectiveness of fluoride dentifrices. The agency indicated that these ranges are intended for formulation purposes and not as a variation for quality control purposes.

The agency also acknowledges that changes in specific gravity result in a corresponding change in the amount of fluoride contained in a given volume of dentifrice if the concentration of the fluoride is expressed as a weight-to-weight measurement, such as ppm.

The agency also indicated that a fluoride range of 0.935 to 1.955 mg per mL of dentifrice might be appropriate. These weight-to-volume measurements correspond directly to allowable ranges for specific gravity (1.1 to 1.7) and theoretical total fluorine (850 to 1,150 ppm). The agency presented the following guidelines for dentifrices: The lower limits of 850 ppm theoretical total fluorine and a specific gravity of 1.1 convert to a lower limit of 0.935 mg fluoride per mL toothpaste. The upper limits of 1,150 ppm theoretical total fluorine and a specific gravity of 1.7 convert to an upper limit of 1.955 mg fluoride per mL toothpaste. This provides a range of 0.935 to 1.955 mg fluoride per mL toothpaste. This range ensures that fluoride dentifrices with different specific gravities, due to changes in the abrasive system, will contain the same range of total fluoride per volume of dentifrice as specified in the LTP tables. This fluoride range also will provide flexibility to accommodate the development of new abrasive systems.

The agency indicated in an earlier comment (see section I.B., comment 10 of this document) that it is including extra-strength sodium monofluorophosphate dentifrices (1,500 ppm) in this final monograph as generally recognized as safe and effective dentifrice products. Therefore, the agency is also providing a range of 1.65 to 2.55 mg per mL of dentifrice for higher strength dentifrices (1,500 ppm). This range corresponds directly to the allowable ranges for specific gravity (1.1 to 1.7).

The agency concludes that fluoride ranges of 0.935 to 1.955 mg (for all 850 to 1,150 ppm dentifrices) and 1.6 to 2.55 mg (for 1,500 ppm sodium monofluorophosphate dentifrices) theoretical total fluorine per mL toothpaste are appropriate for these Category I fluoride dentifrice formulations, irrespective of their specific gravity. The agency is including these ranges in the revised LTP tables. (See also section I.F., comment 37 of this document.)

40. Several comments addressed the use of LTP's, rather than clinical trials, to predict the anticaries effectiveness of monograph fluoride dentifrices formulated with "new" abrasive systems or with anticalculus agents. One comment (from a professional

dental association) objected to the agency's proposal in the tentative final monograph (53 FR 22430 at 22442) to allow LTP's for this testing. The comment contended that all fluoride-containing dentifrice products should either be clinically tested or should be equivalent to clinically tested products. The comment stated that the agency's proposed LTP's would permit marketing of any dentifrice product containing an established fluoride agent regardless of whether or not the abrasive system had been clinically tested. The comment argued that, because of the very limited nature of the monograph LTP's, there is no assurance of the availability of fluoride ions during the time of brushing. The comment added that abrasives can play a very critical role in the rate of release/availability of the active ingredient. Furthermore, the comment stated that the LTP's proposed in the tentative final monograph assess the steady state level of release of the active species. This value, according to the comment, has no meaning in examining the potential efficacy of fluoride dentifrice products. The comment maintained that only clinically tested fluoride/abrasive systems should be eligible for review under the OTC drug monograph system. The comment added that any fluoride dentifrice with an untested abrasive system should be required to supply clinical data demonstrating effectiveness. The comment stated that its association had established testing guidelines designed to demonstrate equivalency of fluoride agents provided that the formulations have a fluoride/abrasive system similar to a clinically effective product.

The comment also contended that fluoride dentifrices containing agents that inhibit calculus formation, thus influencing the calcification/decalsification process associated with caries, should be required to submit a more extensive LTP than the agency had proposed in the tentative final monograph (53 FR 22430 to 22448). The comment recommended that either animal caries or remineralization studies be required for these products. The comment stated that such studies would evaluate the potential inactivation of the fluoride agent by a secondary nontherapeutic additive.

A comment from a manufacturers' association objected to the first comment's position, contending that no data or other information were submitted to rebut the agency's LTP proposal. The comment also disagreed with the dental association's contention that calculus inhibiting agents can influence the calcification/

decalsification process associated with caries. The comment submitted three clinical studies (Refs. 1, 2, and 3) to demonstrate that the inclusion of anticalculus agents in fluoride-containing dentifrices does not interfere with the anticaries effectiveness of these products. The comment noted that three clinically proven anticalculus agents (pyrophosphate salts, zinc chloride, and zinc citrate) are currently marketed in dentifrices in the United States. According to the comment, these agents have been shown not to adversely affect fluoride activity in three biological tests that were included in the tentative final monograph (53 FR 22430 at 22447). The comment objected to the dental association's position concerning the validity of using LTP's to predict the anticaries effectiveness of fluoride dentifrices with an anticalculus agent, contending that the dental association's concern is not warranted by existing scientific data. The comment indicated that it would be a waste of scarce resources and funds to require further clinical testing when laboratory tests can accurately determine whether or not anticalculus agents interfere with fluoride efficacy. The comment requested that the agency continue to require only LTP's as set forth in the tentative final monograph (53 FR 22430 at 22434).

The agency recognizes that inactive ingredients, such as abrasives and anticalculus agents, can play an important role in the rate of release/availability of fluoride from a fluoride compound during the time period of toothbrushing. Although the analytical tests do not directly measure the availability of fluoride ions during the time of toothbrushing, the biological tests indicate that the fluoride ion is active in preventing dental caries. In addition, one of the biological tests, the animal caries reduction, directly measures the anticaries effectiveness of a fluoride dentifrice product in an animal model in vivo after a limited brushing time. The severity of caries in each group is computed, and a favorable result for the test sample indicates that the fluoride ion has activity. The test sample is compared with a U.S.P. fluoride dentifrice reference standard that has been proven effective in clinical studies.

In the tentative final monograph (53 FR 22430 at 22433 and 22440, comments 4 and 11), the agency discussed why lengthy clinical trials are no longer warranted. The comments did not provide any new data or information to alter that conclusion. The agency determined that appropriate laboratory testing, including biological testing, is

adequate to ensure the effectiveness of dentifrices containing monograph fluoride ingredients. The agency indicated that the Panel based its development of LTP's on laboratory testing results from studies on fluoride dentifrice formulations that had actually been clinically tested and found effective. The agency agreed with the Panel's view that a monograph fluoride ingredient/abrasive system in a dentifrice formulation not specifically reviewed by the Panel, must contain an amount of available fluoride ion equal to or greater than the highest available fluoride ion value recommended for the specific fluoride ingredient. This requirement applies to fluoride dentifrices that contain a monograph fluoride ingredient and either (1) a new abrasive ingredient (not previously included in marketed dentifrices) or (2) an abrasive ingredient included in previously marketed dentifrices in a combination not specifically reviewed by the Panel (53 FR 22430 at 22441). The agency proposed that fluoride dentifrices must meet or exceed the soluble fluoride ion level specified for each particular fluoride ingredient listed in the monograph and meet the test requirements of any two of the following biological tests: (1) Enamel solubility reduction (ESR), (2) fluoride uptake by enamel, and/or (3) animal caries reduction (53 FR 22430 at 22434).

The agency does not agree that one of the clinical studies (Ref. 1) submitted by one comment adequately demonstrates whether or not an anticalculus additive affects the anticaries effectiveness of a dentifrice. The study did not include a positive control (Category I) fluoride toothpaste in the experimental design. Instead, a fluoride/anticalculus dentifrice was compared to a negative control toothpaste (not containing either fluoride or anticalculus agent). However, the two other studies (Refs. 2 and 3) submitted by the comment clearly indicate that the anticaries effectiveness of the dentifrice formulations tested was not adversely affected by the anticalculus agents used in the studies. In one study (Ref. 2), three dentifrices containing 1,000, 1,500, or 2,500 ppm fluoride (as sodium monofluorophosphate) and an anticalculus agent (0.5 percent zinc citrate trihydrate) were compared with dentifrices that contained the same fluoride concentrations but no anticalculus agent. At the conclusion of the 3-year study, no clinically significant difference was observed between the fluoride dentifrices with or without the anticalculus agent. However, a dose-response effect was

observed at varying fluoride concentrations. In the other clinical study (Ref. 3), three dentifrices containing 1,000 or 1,100 ppm of fluoride (as sodium fluoride and sodium monofluorophosphate) and different anticalculus ingredients (3.3 percent soluble pyrophosphate, 2 percent zinc chloride, and 1.25 percent unspecified zinc compound) were evaluated. The three dentifrices produced anticaries protection similar to a control sodium monofluorophosphate toothpaste containing 1,000 ppm fluoride, but without an anticalculus ingredient. These two clinical studies corroborate that these anticalculus agents do not interfere with the anticaries effectiveness of the fluoride active ingredients sodium fluoride and sodium monofluorophosphate.

The agency is concerned that newer abrasives and anticalculus agents may reduce the availability of fluoride ions, and that this reduction may not be detected by the chemical tests suggested in the LTP's. These chemical tests may not always reflect the true anticaries effectiveness of fluoride dentifrices with or without additives in situ when diluted in the mouth by saliva or exposed to the subtle reactions between dentifrice ingredients and salivary components. Although these in vitro tests may show positive results that are predictive of anticaries activity, during actual use in the mouth the product may not provide the same expected level of anticaries effectiveness. The limitations of in vitro tests are particularly significant in evaluating fluoride toothpastes that contain additives that may affect fluoride ion availability under in situ conditions. For that reason, the agency considers them to be only markers of potential effectiveness, not actual proof.

During one study (Ref. 4), several laboratory tests (including ESR, enamel uptake of fluoride, and animal caries reduction tests) were investigated as indicators of the compatibility of an abrasive system and a fluoride source. Dentifrices containing 1,000 ppm of fluoride (as sodium fluoride, stannous fluoride, or sodium monofluorophosphate) were formulated with abrasives known either to interact or not interact with particular fluorides. The in vitro tests measured fluoride uptake for a considerably longer time period than would be experienced during actual intermittent use. The authors claimed that the in vitro tests provide valuable information. They also stated that the results of the ESR test did not correlate well with the animal caries assay results. Furthermore, the authors noted that the sodium

monofluorophosphate dentifrices provided high levels of available active fluoride ions but produced only small reductions in enamel solubility. Thus, this study indicated that the animal caries reduction studies gave the most complete assessment of effectiveness of the dentifrices tested compared with the test results from the two in vitro tests (ESR and enamel uptake of fluoride). Therefore, the agency concludes that both animal and human studies provide a more complete assessments of anticaries effectiveness.

The agency has thoroughly reviewed the comments, the clinical studies involving anticalculus agents added to dentifrice products containing monograph fluoride ingredients, and data comparing the results of in vitro biological tests with in vivo animal caries tests. Based on this evaluation, the agency concludes that biological testing is necessary for all clinically untested dentifrice products to ensure fluoride ion availability. Therefore, the agency is revising the biological testing requirements in this final monograph to require that all OTC anticaries dentifrice drug product formulations not specifically reviewed by the Panel be tested in an animal caries reduction test. This type of biological test will be required rather than optional, as proposed in the tentative final monograph (53 FR 22430 at 22434). Based upon a review of all the available data, the agency still concludes that long-term clinical trials are not needed for different or new dentifrice products containing a monograph fluoride ingredient/abrasive system, including untested abrasive systems or new additives. The agency considers fluoride availability as well as ESR and fluoride uptake studies to be good predictors of potential effectiveness of a fluoride toothpaste. However, the in vivo animal caries reduction test provides further assurance that the dentifrice is active against dental caries. The biological portion of the recommended testing provides an important assurance that, in addition to being chemically available as demonstrated by the analytical portion of the testing recommendations, the fluoride is also bioavailable in that it will alter tooth structure in the biological tests to make the tooth resistant to caries.

Accordingly, the agency is revising the first sentence in § 355.70 of the testing procedures for fluoride dentifrice drug products to read: "A fluoride dentifrice drug product shall meet the biological test requirements for animal caries reduction and one of the following tests: Enamel solubility reduction or fluoride enamel uptake."

Although the agency encourages the development of additional testing procedures, such as remineralization tests, the agency considers the three biological tests recommended by the Panel as sufficient at this time to demonstrate anticaries effectiveness. Demineralization/remineralization studies in humans may also be predictive of anticaries effectiveness. However, the agency has not received sufficient data to correlate specifically the results of remineralization tests with clinical studies that demonstrate anticaries effectiveness of fluoride dentifrices. The agency would consider such tests as an option to animal caries reduction tests if adequate data were submitted to the agency in the form of a petition to amend the monograph.

References

- (1) Lu, K. H. et al., "The Effect of a Fluoride Dentifrice Containing an Anticalculus Agent on Dental Caries in Children," *Journal Of Dentistry For Children*, 52(6):449-451, 1985.
 - (2) Stephen, K. W. et al., "A 3-Year Oral Health Dose-Response Study of Sodium Monofluorophosphate Dentifrices with and without Zinc Citrate: Anti-Caries Results," *Community Dentistry and Oral Epidemiology*, 16:321-325, 1988.
 - (3) Triol, C. W. et al., "A Clinical Study of the Anticaries Efficacy of Three Fluoride Dentifrices Containing Anticalculus Ingredients: One and Two Year Results," *The Journal of Clinical Dentistry*, 1(2):48-50, 1988.
 - (4) Pader, M. et al., "The Evaluation of Fluoride Dentifrices," *Journal of the Society of Cosmetic Chemistry*, 28:681-694, 1977.
41. One comment stated that it is unclear what the reference standards will be for the required analytical and biological testing of fluoride dentifrices. The comment contended that it is difficult to comment on the whole program without knowing what the standards are. The comment suggested that an additional period of time be permitted to allow interested groups to comment on the acceptability of the actual United States Pharmacopeia (U.S.P.) reference standards when they are established.
- In the tentative final monograph, the agency stated that it was coordinating establishment of the fluoride dentifrice reference standard formulations with the United States Pharmacopeial Convention (U.S.P.C.) (53 FR 22430 at 22439). Since then, industry has worked with the U.S.P.C. to establish reference standards, through the joint Nonprescription Drug Manufacturers Association and Cosmetic, Toiletry and Fragrance Association task force. Information about the reference standards was made public in U.S.P.'s Pharmacopeial Forum in 1990 (Ref. 1),

and interested parties had an opportunity to comment at that time. Reference standards have been available from U.S.P.C. since 1990.

Based on the public availability and use of these U.S.P. fluoride dentifrice reference standards by the industry since 1990, the agency concludes that it is not necessary to provide an additional comment period.

Reference

(1) The United States Pharmacopeial Convention, Inc., "Headquarters Column," *Pharmacopeial Forum*, 16:3-4, 1990.

42. Two comments requested that the agency refrain from mandating specific biological test procedures in the final monograph for OTC anticaries drug products. Instead, the two comments requested that the biological test procedures proposed in § 355.70 be considered as guidelines only. The comments agreed with the agency that the substitution of a new test, such as remineralization, for one of the three qualifying biological tests should require a petition for FDA approval. However, the comments strongly disagreed with the need for a petition for minor modifications in the biological testing protocols when the results are at least as valid, reliable, and accurate as the current test procedures. One comment added that, without this flexibility, the acceptance by the agency of even minor changes may take an inordinate period of time without helping to protect the dentifrice user from an ineffective product. The comment suggested that if the agency continues to maintain control over changes in test procedures, approval of the changes should be timely and a list of criteria should be provided so that manufacturers can be assured that changes will be accepted by the agency.

The second comment indicated that mandating specific test protocols tends to discourage scientific experimentation and the application of advanced technology in method development. The comment noted that advances in technology alone will result in changes in test protocols and the precision, sensitivity, and accuracy of various measurements. Therefore, the comment requested that the agency designate the biological testing procedures as guidelines only and explicitly indicate that other valid, reproducible methods are acceptable. The comment indicated that requiring a petition to modify and improve a procedure would not only be time consuming, but also would be expensive and thus not in the interest of consumers. The comment concluded that companies should have the opportunity to make minor modification

to test methods as long as the changes are scientifically validated and produce accurate and reliable results.

The agency does not agree that the specific biological testing procedures for fluoride dentifrices should be considered as test guidelines only. The agency indicated in the tentative final monograph (53 FR 22430 at 22443) that the availability of the fluoride ion in a dentifrice formulation and meeting the biological testing requirements are the most important testing criteria for predicting the effectiveness of a fluoride dentifrice product. The agency considers demonstration of the bioavailability of the fluoride ion in the biological tests listed in § 355.70 as necessary to ensure the anticaries effectiveness of fluoride dentifrices. The agency points out that the required biological tests are based on the results of actual biological testing procedures performed on fluoride dentifrices that had been shown to be clinically effective in preventing caries. These testing procedures are a regulatory standard that supports general recognition of the safety and effectiveness of fluoride dentifrices.

The agency has had a similar petition procedure for many years for modifications to the in vitro test for OTC antacid drug products (see 21 CFR 331.29). The agency has processed these petitions in a timely manner. Accordingly, the agency is including the biological testing procedures in § 355.70 as required tests for any fluoride dentifrice drug product marketed pursuant to this monograph.

The agency finds no basis to agree with the comment's suggestion that requiring these specific biological testing procedures interferes with the advancement of science and technology. The agency does not intend for the testing procedures to preclude the application of new, advanced technology in testing fluoride dentifrices. The agency agrees with the two comments that as technology continues to evolve, modifications to the existing testing procedures may result in more sensitive, reliable, and accurate measurements. However, there should be a consensus in the scientific community that these new procedures are generally accepted. The agency encourages the development of new testing technology and methods for fluoride dentifrices and has provided in the monograph the opportunity for interested persons to propose modifications or alternative testing procedures through the petition process in 21 CFR 10.30. Any petition should contain sufficient data to support the modification and to demonstrate that

the alternative testing procedure provides results that are equivalent to the currently required biological test methods.

43. Two comments objected to fluoride dentifrice reference standards being provided through the U.S.P.C. The comments suggested that exact specifications for these reference standards (including levels of ingredients, source of raw materials, product specifications, and detailed production directions) be provided as part of the U.S.P. monograph system so that manufacturers could prepare their own fresh reference standards when needed. One comment contended that, given sufficient detailed specifications, manufacturers would certainly be as qualified to produce properly prepared standards as the U.S.P.C.

Following publication of the tentative final monograph, FDA and industry developed procedures for introduction of new or modified commercial dentifrice formulations without full clinical testing, provided that bioavailability/bioequivalence of the formulation was demonstrated against an appropriate reference standard (Ref. 1). Six U.S.P. fluoride dentifrice reference standards were initially established for use in the biological testing of fluoride dentifrices: (1) Sodium fluoride-calcium pyrophosphate (high beta-phase), (2) sodium fluoride-silica, (3) sodium monofluorophosphate-calcium carbonate, (4) sodium monofluorophosphate-dicalcium phosphate, (5) sodium monofluorophosphate-silica, (6) stannous fluoride-silica (Ref. 2). These reference standards are prepared by manufacturers of dentifrice drug products and provided to the U.S.P.C. for distribution. Thus, the agency agrees with one comment that manufacturers are qualified to produce these reference standards. Based on the development of these reference standards by manufacturers of OTC dentifrice drug products, neither the agency nor the U.S.P.C. sees a need to include exact specifications for these reference standards in the U.S.P. monograph system. Furthermore, the U.S.P. monograph system does not include exact specifications for other reference standards the U.S.P.C. provides.

The agency had a meeting with U.S.P.C. and industry representatives on May 20, 1993 (Ref. 3), to discuss the existing U.S.P. program for dentifrice reference standards and to determine if any changes were needed once the final monograph for OTC anticaries drug products is issued. Additional procedures to assure continued

availability of these dentifrice reference standards from the U.S.P.C. were developed. The U.S.P.C.'s current supply of dentifrice reference standards were subsequently tested to monitor stability (Refs. 4 through 7). Manufacturers of each reference standard have committed to retest stability every 18 months and to make every effort to resupply the U.S.P.C. with additional reference standards when supplies are depleted (Ref. 3). This should occur within 1 to 2 months after the U.S.P.C. makes a request. The U.S.P.C. will provide information concerning the reference standards' stability profile (including total fluoride, available fluoride ions, pH, and specific gravity) that is provided by each manufacturer to any purchaser upon written request. The agency believes that the availability of this information adequately addresses the comments' concerns about specifications for these dentifrice reference standards. Other information of concern, such as source of raw materials and detailed production directions, are considered confidential commercial information or trade secret information. The agency concludes that distribution of dentifrice reference standards by the U.S.P.C. is appropriate.

References

- (1) The United States Pharmacopeial Convention, Inc., "Headquarters Column," *Pharmacopeial Forum*, 16:3-4, 1990.
 - (2) The United States Pharmacopeial Convention, Inc., "Reference Standards Catalog," *Pharmacopeial Forum*, 17:2458, 1991.
 - (3) Minutes of meeting between FDA, U.S.P.C., and industry representatives, May 20, 1993, identified as MM6, Docket No. 80N-0042, Dockets Management Branch.
 - (4) Comment No. RPT4, Docket No. 80N-0042, Dockets Management Branch.
 - (5) Comment No. RPT5, Docket No. 80N-0042, Dockets Management Branch.
 - (6) Comment No. RPT6, Docket No. 80N-0042, Dockets Management Branch.
 - (7) Comment No. RPT7, Docket No. 80N-0042, Dockets Management Branch.
44. Two comments suggested that several U.S.P. reference standards for dentifrices should be provided for each Category I fluoride ingredient and abrasive combination for which clinical proof of effectiveness has been submitted. The comments stated that the types and sources of abrasives and other ingredients present in dentifrice reference standards could have a significant effect on the results of bioavailability tests. As an example, the comments suggested that U.S.P. dentifrice reference standards for sodium fluoride products should include sodium fluoride/calcium pyrophosphate, sodium fluoride/silica,

and sodium fluoride/sodium bicarbonate combinations, all of which have been proven effective in clinical trials. According to one comment, providing all of these standards would ensure the exclusion of ineffective combinations without unfairly excluding dentifrices that are effective but fail to meet the performance of an inappropriate standard.

The agency agrees with the comments that the availability of appropriate U.S.P. reference standards is essential to conduct the biological testing included in this final monograph for OTC anticaries drug products. In the tentative final monograph (53 FR 22430 at 22439), the agency stated that it was coordinating with U.S.P.C. to establish fluoride dentifrice reference standards that would be made available to manufacturers interested in manufacturing fluoride dentifrices. Subsequently, U.S.P. fluoride dentifrice reference standards have been established for Category I fluoride ingredient/abrasive combinations that had been reviewed by the Panel and determined by clinical trials to be effective anticaries drug products. These reference standards include the fluoride dentifrice combinations suggested by the comments, i.e., sodium fluoride/calcium pyrophosphate and sodium fluoride/silica, as well as sodium monofluorophosphate/calcium carbonate, sodium monofluorophosphate/dicalcium phosphate, sodium monofluorophosphate/silica, and stannous fluoride/silica (see section I.F., comment 43 of this document). A list of U.S.P. reference standards available as of the date of this final rule is on file in the Dockets Management Branch (Ref. 1).

The U.S.P. reference standards that have been established include only those dentifrice formulations that have been demonstrated to be clinically effective and that were reviewed by the Panel. At the time of the Panel's deliberation, no clinical data supporting the effectiveness of a sodium fluoride/sodium bicarbonate dentifrice were submitted for review. Consequently, a U.S.P. reference standard for this dentifrice formulation has not been established.

The agency indicated in the tentative final monograph (53 FR 22430 at 22443) that any Category I fluoride compound formulated with an appropriate abrasive can be marketed provided the dentifrice meets the biological testing requirements in § 355.70 and contains the amount of available fluoride ion stated in § 355.10. The particular fluoride ingredient contained in the

chosen reference standard must be the same as the fluoride ingredient in the dentifrice formulation being tested; however, it is not necessary that the abrasive be the same as the abrasive contained in the reference standard. The agency is aware that several manufacturers use the U.S.P. reference standards, sodium fluoride/calcium pyrophosphate or sodium fluoride/silica, in the biological testing of their sodium fluoride/sodium bicarbonate dentifrice products (Ref. 2). A manufacturers' association has recently informed the agency that a new supply of one of the U.S.P. reference standards, sodium fluoride/calcium pyrophosphate (high-beta phase), will not be manufactured when the current supply at U.S.P.C. is exhausted (Ref. 3). When this sodium fluoride/calcium pyrophosphate dentifrice reference standard is no longer available, manufacturers should use the sodium fluoride/silica dentifrice reference standard in its place to conduct the biological tests. Thus, in response to the comment's suggestion that a reference standard be established for a sodium fluoride/sodium bicarbonate dentifrice, it is sufficient that the formulation meet the biological testing requirements using a reference standard containing sodium fluoride, and the available fluoride ion concentration of the dentifrice be equal to or greater than 650 ppm.

References

- (1) OTC Vol. 08BTPRS, Docket No. 80N-0042, Dockets Management Branch.
- (2) Memoranda of telephone conversations between C. Martin, FDA, and W. Cooley, Procter & Gamble Co., dated February 8, 1993; P. Okarma, Colgate-Palmolive Co., dated February 9, 1993; and D. Worrell, Church & Dwight Co., dated February 17, 1993, OTC Vol. 08AFM, Docket No. 80N-0042, Dockets Management Branch.
- (3) Comment No. RPT4, Docket No. 80N-0042, Dockets Management Branch.

G. Comments on Package Size Limitation

45. One comment requested that the agency increase the fluoride dentifrice package size limitation from 260 mg of total fluorine per package to 350 mg to accommodate the increased amount of fluoride contained in dentifrices containing 1,500 ppm. The comment noted that dentifrice products marketed pursuant to the proposed OTC drug monograph contain less than 1,150 ppm fluoride and are marketed in 9-oz package sizes to adhere to the 260-mg total fluorine package size limitation. The comment indicated that FDA had obviously reconsidered the 260-mg dentifrice package size limitation in approving an NDA for an OTC dentifrice

product containing 1,500 ppm fluoride. According to the comment, the NDA fluoride dentifrice is marketed in 8.2 and 6.4 oz package sizes that contain 350 and 272 mg theoretical total fluorine, respectively. The comment added that these package sizes do not have any special cautionary labeling concerning the additional fluoride and do not have child-resistant closures. The comment contended that consumers would not be able to differentiate the amount of fluoride contained in packages of the 1,150-ppm and the 1,500-ppm products, and thus would not treat or use the products differently. The comment remarked that there appears to have been no concern at all that ingestion of the entire package of dentifrice was a real public safety risk. The comment concluded that consumers would benefit from an increase in the package size fluorine limitation because of the added convenience of a larger package size and more economical products on a cost per oz basis.

The comment stated that the issue in establishing a package size limitation is to prevent acute toxicity that may result from a single individual ingesting the entire contents of a fluoride dentifrice package on a single occasion, rather than to prevent the long-term adverse effects of fluoride ingestion. The comment submitted a list of 21 published animal toxicology studies (Ref. 1) that were submitted in support of the NDA for the 1,500-ppm fluoride dentifrice product. The comment stated that a review of its marketing experience records over an 18-month period (during which tubes as small as 1.4 oz were marketed) indicated that no one in the United States had ingested an entire tube of toothpaste regardless of size during that period of time. The comment added that it has marketed a 1,450-ppm fluoride (theoretical total fluorine) dentifrice extensively outside the United States in tube sizes that exceed the proposed monograph package size limitations without any special warnings or closures. The comment stated that no incidents or issues have been raised with respect to the safety of such package sizes. The comment concluded that the proposed 260-mg package size limitation is unnecessary to protect the safety or health of the American public and that the limitation should be raised to 350-mg.

After the tentative final monograph was published in 1985, the agency evaluated and approved an NDA (19-518) for an OTC fluoride dentifrice containing 1,500-ppm theoretical total fluoride (Ref. 2). As part of that evaluation, the agency reconsidered, as noted by the comment, the package size limitation of 260 mg total fluorine that had been recommended by the Panel and proposed by the agency in the tentative final monograph. The agency approved marketing of a 6.4 oz (actually containing 276 mg total fluorine) and a 8.2 oz (containing 350 mg total fluorine) package size. Since that time, the agency has reviewed the confidential sales distribution data submitted under the NDA for the extra-strength dentifrice. The data indicate extensive marketing experience for the 6.4 oz package size and limited marketing of the 8.2 oz package size. Furthermore, the manufacturer of the extra-strength dentifrice has discontinued marketing the 8.2 oz package size (Ref. 3). The agency concludes that it has insufficient marketing experience and an inadequate safety profile to support general recognition of an 8.2 oz package size containing 350 mg total fluorine per package. The agency has sufficient data to support the 6.4 oz package size of 1,500 ppm dentifrice (containing 276 mg total fluorine). Therefore, the agency is limiting monograph dentifrices to a package size containing no more than 276 mg total fluorine per package.

References

- (1) Comment No. CP4, Docket No. 85N-0554, Dockets Management Branch.
- (2) Copy of FDA-approved Labeling from NDA 19-518, OTC Vol. 08AFM, Docket No. 80N-0042, Dockets Management Branch.
- (3) Memorandum of telephone conversation between C. Martin, FDA, and L. Cancro, Consultant to Chesebrough-Pond's Co., dated August 9, 1993, OTC Vol. 08AFM, Docket No. 80N-0042, Dockets Management Branch.

46. One comment requested that the proposed package size limitations for dentifrices, treatment rinses, and treatment gels in § 355.20(a) and (b) not be limited to 260 mg (dentifrices) and 120 mg (rinses and gels) total fluorine per package when the products are intended for professional use. Noting that the package size limitations were proposed because of potential toxicity that might be caused by accidental ingestion of these products, the comment contended that these package

size restrictions are inappropriate for professional packages used by dental practitioners in their practice. The comment stated that dentists routinely administer these products to their patients as part of their treatment and, thus, require a larger container than the proposed OTC package sizes. The comment concluded that professional package sizes would have limited distribution, would not be available to consumers and, therefore, would not be a safety concern.

The package size limitations established for OTC fluoride dentifrices, treatment rinses, and preventive treatment gels in § 355.20 of this final monograph are intended for products used by the general public and not for products used only under professional supervision. The agency does not believe that safety problems will occur when a larger package size is distributed for professional office use only, provided the package is not intended to be distributed by the dentist to the consumer for home use. A product marketed in this manner would present potential safety problems similar to an OTC product. Therefore, the agency is not limiting the package size for dentifrices, treatment rinses, and preventive treatment gels labeled for professional office use only. The agency is including in § 355.60 of the monograph (professional labeling) the following statements for products marketed to health professionals in package sizes larger than those specified in § 355.20: "For Professional Office Use Only" and "This product is not intended for home or unsupervised consumer use." For clarity, the agency is adding paragraph (a)(3) to § 355.20 as follows: "Package size limitations do not apply to anticaries drug products marketed for professional office use only and labeled in accord with § 355.60."

II. Summary of Significant Changes From the Proposed Rule

A. Summary of Ingredient Categories

The agency has reviewed all claimed active ingredients submitted to the Panel and to the tentative final monograph, as well as other data and information available at this time. For the convenience of the reader, the following table is a summary of the agency's categorization of OTC anticaries active ingredients.

Anticaries Active Ingredients	Monograph (M)	Nonmonograph (NM)
Hydrogen fluoride:		

Anticaries Active Ingredients	Monograph (M)	Nonmonograph (NM)
Rinse—In an appropriate formulation with 0.02 percent fluoride ion		NM
Phosphate preparations:		NM
Calcium sucrose phosphate		NM
Dicalcium phosphate dihydrate		NM
Disodium hydrogen phosphate		NM
Phosphoric acid		NM
Sodium dihydrogen phosphate		NM
Sodium dihydrogen phosphate monohydrate		NM
Sodium phosphate		NM
Sodium phosphate, dibasic anhydrous reagent		NM
Sodium bicarbonate		NM
Sodium fluoride:		
Dentifrice—paste: 0.188 to 0.254 percent (with ≤ 650 available fluoride ion)	M	
Dentifrice—powder: 0.188 to 0.254 percent (with ≥ 850 ppm available fluoride ion and poured-bulk density of 1.0 to 1.2 g/mL)	M	
Rinse—0.05 percent	M	
Rinse—0.02 percent	M	
Rinse—Acidulated phosphate fluoride with 0.02 percent fluoride ion	M	
Rinse—Acidulated phosphate fluoride with 0.01 percent fluoride ion	M	
Sodium fluoride and hydrogen fluoride:		
Rinse—Acidulated phosphate fluoride with 1.23 percent fluoride ion		MN
Sodium monofluorophosphate (850 to 1,150 ppm):		
Dentifrice: 0.654 to 0.884 percent (with ≥ 800 ppm available fluoride ion as PO ₃ F ⁻ and F ⁻ combined)	M	
Rinse—6.0 percent		NM
Sodium monofluorophosphate (1,500 ppm):		
Dentifrice—1.153 percent (with ≥ 1,275 ppm available fluoride ion as PO ₃ F ⁻ and F ⁻ combined)	M	
Stannous fluoride:		
Dentifrice—0.351 to 0.474 with an available fluoride ion concentration of:		
≥ 700 ppm for products containing abrasive other than calcium pyrophosphate	M	
or		
≥ 290 ppm for products containing the abrasive calcium pyrophosphate	M	
Rinse—0.1 percent	M	
Gel—0.4 percent in an anhydrous glycerin gel	M	

B. Summary of the Agency's Changes

1. The agency is revising the definitions proposed for anticaries drug, dentifrice, and treatment gel in § 355.3(c), (e), and (i), respectively. The agency is adding a definition for anhydrous glycerin in § 355.3(b), as used in § 344.3(a) (21 CFR 344.3(a)) of the final monograph for OTC topical otic drug products. Also, in § 355.3(h), the agency is adding a definition for a fluoride supplement that is intended to be swallowed. Because of these additions, proposed § 355.3(b) through (f) have been redesignated as paragraphs (c) through (g), and § 355.3(g) through (k) have been redesignated as paragraphs (i) through (m), respectively, in this final monograph. (See section I.B., comments 5, 6, and 7 of this document.)

2. The agency is including fluoride dentifrices that contain 1,500 ppm theoretical total fluorine in § 355.10(b)(2) of this final monograph. Because of concerns about dental fluorosis, the agency is requiring that dentifrices containing these fluorine concentrations be clearly labeled for use only by children 6 years of age and older and is including directions for adults and children 6 years of age and older in § 355.50(d)(1)(ii) of this final monograph. The agency is also including an optional additional labeling statement that will inform consumers of the benefits of these products. (See section I.B., comment 10 of this document.)

3. The agency is adding sodium fluoride/sodium bicarbonate powdered dentifrices in § 355.10(a)(2) of this final monograph. Directions for these

products appear in § 355.50(d)(1)(iii). (See section I.B., comments 13 and 14 of this document.)

4. The agency is increasing the package size limitations in § 355.20(a) for dentifrice (toothpastes and tooth powders) packages up to 276 milligrams total fluorine per package. The agency is also adding a new paragraph in § 355.20 for fluoride powdered dentifrices that provides for tight container packaging in accordance with the definition in the U.S.P. (See section I.B., comment 15 and section I.G., comment 45 of this document.)

5. The agency notes that there is a U.S.P. monograph for Sodium Fluoride and Phosphoric Acid Topical Solution (Ref. 1). This monograph applies to acidulated phosphate sodium fluoride topical solutions having a pH between 3.0 and 4.0. Therefore, this monograph

would apply to the aqueous solution of acidulated phosphate fluoride described in § 355.10(a)(3)(ii) of the final monograph for OTC anticaries drug products and could apply to the aqueous solution of acidulated phosphate fluoride described in § 355.10(a)(3)(i) if the pH range of the U.S.P. monograph were to be expanded to 4.5. The agency and an interested manufacturer (Ref. 2) are working with U.S.P. to develop a revision in the compendial monograph for these rinse

products. The agency anticipates that this revision will be completed before this final monograph for OTC anticaries drug products becomes effective. In accord with § 355.50(a) of the final monograph, manufacturers marketing these products should include the compendial name, Sodium Fluoride and Phosphoric Acid Topical Solution, as the established name in the labeling of such products.

References

- (1) *The United States Pharmacopeia 23—The National Formulary 18*, United States Pharmacopeial Convention, Inc., Rockville, MD, p. 1423, 1994.
 - (2) Memorandum of telephone conversation between C. Martin, FDA, and P. Okarna, Colgate-Palmolive Co., dated December 9, 1993, OTC Vol. 08AFM, Docket No. 80N-0042, Dockets Management Branch.
6. The agency is redesignating several paragraphs and is providing the following table of changes for the convenience of the reader:

Paragraph number in this final monograph	Paragraph number in the tentative final monograph
355.3(b)	
355.3(c) through (g)	
355.3(h)	355.3(b) through (f)
355.3(i) through (m)	355.3(g) through (k)
355.10(a)(2)	
355.10(a)(3)(i)	
355.10(a)(3)(ii)	355.10(b)(1)
355.10(a)(3)(iii)	355.10(b)(2)
355.10(a)(3)(iv)	355.10(b)(3)
355.10(a)(3)(v)	355.10(b)(4)
355.10(b)(1)	355.10(b)(5)
355.10(b)(2)	355.10(a)(2)
355.10(c)(1)(i)	
355.10(c)(1)(ii)	355.10(a)(3)
355.10(c)(2)	355.10(a)(4)
355.10(c)(3)	355.10(c)
	355.10(b)(6)
355.20(a)(1) ¹	
355.20(a)(2)	355.20(a)
355.20(a)(3)	355.20(b)
355.20(b)	
355.50(d)(1)(i)	
355.50(d)(1)(ii)	355.50(d)(1)(i)
355.50(d)(2)(i)	
355.50(d)(2)(ii)	355.50(d)(2)
355.50(d)(2)(iii)	
355.50(d)(5)	355.50(d)(2)(ii)
355.50(e)(2)	
355.50(f)(1) ²	355.50(e)(3)
355.50(f)(2)	355.50(f)
	355.50(g)

¹ Because § 355.20(b) has been revised, the heading of § 355.20 has been changed to "Packaging conditions."

² Because § 355.50(f)(2) has been added, the word "statement" in the heading of § 355.50(f) has been changed to "statements."

7. The agency is revising and expanding § 355.50(a) to provide the option of using the additional terms "mouthwash," "tooth powder," and "tooth polish" in the statement of identity. The agency is also requiring that the term "preventive treatment" be included in the statement of identity for nonabrasive fluoride gels. The agency is providing that the word "treatment" be optional in the statement of identity for fluoride rinse products. (See section I.C., comments 17 and 18 of this document.)

8. The agency has moved the statement "Do not use before mixing with water" from the warnings in proposed § 355.50(c) to the directions for use in § 355.50(d)(5) of this final monograph. This statement is to be the first sentence of the directions for concentrated treatment rinse solutions, powders, and effervescent tablets. (See section I.C., comment 26 of this document.)

9. The agency is modifying the general warning in § 330.1(g), which states: "Keep this and all drugs out of the reach of children," to read as

follows for fluoride dentifrice drug products: "Keep out of the reach of children under 6 years of age." This warning appears in § 355.50(c)(1) of this final monograph. However, in § 355.50(c)(2), the agency continues to require the general warning in § 330.1(g) for all other OTC anticaries drug products. (See section I.B., comment 22 of this document.)

10. The agency is revising the directions for anticaries dentifrice drug products proposed in § 355.50(d) and is including the revised directions in § 355.50(d)(1)(i), (d)(1)(ii), and (d)(1)(iii).

of this final monograph. The agency is also revising the directions for use of anticaries preventive treatment gels by children in § 355.50(d) to read: "Instruct children under 12 years of age in the use of this product (to minimize swallowing). Supervise children as necessary until capable of using without supervision." The agency is including the revised directions in § 355.50(d)(4) in this final monograph.

11. The agency is revising the directions for use of anticaries treatment rinses by children, proposed in § 355.50(d)(2)(i), to read: "Instruct children under 12 years of age in good rinsing habits (to minimize swallowing). Supervise children as necessary until capable of using without supervision." The agency is including the revised directions in § 355.50(d)(2)(i) and (d)(2)(ii) in this final monograph. (See section I.C., comment 25 of this document.)

12. The agency is not including proposed § 355.50(e)(2) in this final monograph. In its place, the agency is including new § 355.55, as follows: "*Principal display panel of all fluoride rinse drug products.* In addition to the statement of identity required in § 355.50, the following statement shall be prominently placed on the principal display panel: **IMPORTANT: Read directions carefully before using**". Because proposed § 355.50(e)(2) is not included in this monograph, the agency is redesignating proposed § 355.50(e)(3) as § 355.50(e)(2) in this final monograph. (See section I.C., comment 20 of this document.)

13. The agency is not including proposed § 355.50(g) (which states: "The word 'physician' may be substituted for the word 'doctor' in any of the labeling statements in this section.") in this final monograph because the agency has amended § 330.1 to permit the interchangeability of certain terms, including "physician" and "doctor," in all OTC drug monographs. (See 59 FR 3998, January 28, 1994.)

14. The agency is modifying the introductory language in the professional labeling in § 355.60 to read: "The labeling for anticaries fluoride treatment rinses identified in § 355.10(b) that are specially formulated so they may be swallowed (fluoride supplements) and are provided to health professionals (but not to the general public) may contain the following additional dosage information: * * *" (See section I.C., comment 28 of this document.)

15. The agency is including in § 355.60 (professional labeling) the following statements for products

marketed to professionals in package sizes larger than those specified in § 355.20: "For Professional Office Use Only" and "This product is not intended for home or unsupervised consumer use." The agency is also amending § 355.20 by revising paragraph (b) to read: "Package size limitations do not apply to anticaries drug products marketed for professional office use only and labeled in accord with § 355.60." (See section I.G., comment 46 of this document.)

16. The agency is revising the biological testing requirements in this final monograph to require that all OTC anticaries dentifrice drug product formulations be tested in an animal caries reduction test rather than allowing this type of biological test to be optional as proposed in the tentative final monograph (53 FR 22430 at 22434). Accordingly, the first sentence in § 355.70 of the testing procedures for fluoride dentifrice drug products reads: "A fluoride dentifrice drug product must meet the biological test requirements for animal caries reduction and one of the following tests: Enamel solubility reduction or fluoride enamel uptake." The agency has further revised the proposed testing guidance for parameters other than available fluoride ion and biological test requirements and is citing these revised parameters as testing intended as guidance, e.g., for use in determining expiration dating. The agency is including a revised LTP chart in the preamble of this document for informational purposes. (See section I.F., comments 37, 39, and 40 of this document.)

17. The agency is revising the testing procedures in § 355.70 to include information about the available U.S.P. fluoride dentifrice reference standards. (See section I.F., comments 43 and 44 of this document.)

III. The Agency's Final Conclusions on OTC Anticaries Drug Products

Based on available evidence, the agency is issuing a final monograph establishing conditions under which OTC anticaries drug products (aid in the prevention of dental cavities) are generally recognized as safe and effective and not misbranded. Specifically, the agency has determined that the following active ingredients meet monograph conditions: Sodium fluoride, sodium monofluorophosphate, and stannous fluoride. All other ingredients considered in this rulemaking have been determined to be nonmonograph conditions. Four of these ingredients are presently listed in § 310.545(a)(2) (21 CFR 310.545(a)(2)) as

not generally recognized as safe and effective for anticaries use, i.e., hydrogen fluoride, sodium carbonate, sodium monofluorophosphate (6 percent rinse), and sodium phosphate. In this final rule, the agency is amending § 310.545(a)(2) by adding the ingredients calcium sucrose phosphate, dicalcium phosphate dihydrate, disodium hydrogen phosphate, phosphoric acid, sodium dihydrogen phosphate, sodium dihydrogen phosphate monohydrate, and sodium phosphate, dibasic anhydrous reagent to this list of nonmonograph conditions. These ingredients appear in new § 310.545(a)(2)(ii), while previous § 310.545(a)(2) is redesignated § 310.545(a)(2)(i).

The agency is removing the existing warning and caution statement required in § 369.21 (21 CFR 369.21) and exemptions for certain drugs limited by NDA's to prescription sale in § 310.201(a)(10) and (a)(15) (21 CFR 310.201(a)(10) and (a)(15)) for anticaries drug products because most portions of those regulations are superseded by the anticaries final monograph (21 CFR part 355). The items being removed include: (1) § 310.201(a)(10)(i) through (a)(10)(vi); (2) § 310.201(a)(15)(i) through (a)(15)(vi); and (3) paragraphs in § 369.21 applicable to sodium fluoride dentifrice powder and sodium monofluorophosphate dentifrice solution. The agency is reserving paragraphs (a)(10) and (a)(15) in § 310.201 for future use.

Any drug product labeled, represented, or promoted for use as an OTC anticaries drug product that contains any of the ingredients listed in § 310.545(a)(2) or that is not in conformance with the monograph (21 CFR part 355) may be considered a new drug within the meaning of section 201(p) of the act (21 U.S.C. 321(p)) and misbranded under section 502 of the act (21 U.S.C. 352) and may not be marketed for this use unless it is the subject of an approved application or abbreviated application under section 505 of the act (21 U.S.C. part 355) and part 314 of the regulations (21 CFR part 314). In appropriate circumstances, a citizen petition to amend the monograph may be submitted under 21 CFR 10.30 in lieu of an application. Any OTC anticaries drug product initially introduced or initially delivered for introduction into interstate commerce after the effective dates of § 310.545(a)(2) or the effective date of this final rule that is not in compliance with the regulations is subject to regulatory action.

An analysis of the cost and benefits of this regulation, conducted under

Executive Order 12291, was discussed in the tentative final monograph of September 30, 1985 (50 FR 39854) and in the amendment of the tentative final monograph of June 15, 1988 (53 FR 22430). No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (50 FR 39854 at 39871, and 53 FR 22430 at 22447), and the substance of that analysis has not changed. Executive Order 12291 has been superseded by Executive Order 12866. FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96-354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order and, thus, is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. All major anticaries drug products already contain monograph ingredients, and no reformulations should be necessary. This final rule will require some relabeling for these products. Manufacturers will have 1 year to implement this relabeling. Accordingly, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

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

List of Subjects

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 355

Labeling, Over-the-counter drugs.

21 CFR Part 369

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

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR chapter I is amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512-516, 520, 601(a), 701, 704, 705, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b-360f, 360j, 361(a), 371, 374, 375, 379e); secs. 215, 301, 302(a), 351, 354-360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b-263n).

§ 310.201 [Amended]

2. Section 310.201 *Exemption for certain drugs limited by new-drug applications to prescription sale* is amended by removing and reserving paragraphs (a)(10) and (a)(15).

3. Section 310.545 is amended by redesignating the text of paragraph (a)(2) as paragraph (a)(2)(i); by adding new (a)(2)(i) heading and paragraphs (a)(2)(ii) and (d)(24); and by revising paragraph (d) introductory text and paragraph (d)(1) to read as follows:

§ 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.

- (a) * * *
- (2) *Anticaries drug products—(i)*
*Approved as of May 7, 1991. * * **
(ii) Approved as of October 7, 1996.
Calcium sucrose phosphate
Dicalcium phosphate dihydrate
Disodium hydrogen phosphate¹
Phosphoric acid¹
Sodium dihydrogen phosphate
Sodium dihydrogen phosphate monohydrate
Sodium phosphate, dibasic anhydrous reagent¹

(d) Any OTC drug product that is not in compliance with this section is subject to regulatory action if initially introduced or initially delivered for introduction into interstate commerce after the dates specified in paragraphs (d)(1) through (d)(24) of this section.

(1) May 7, 1991, for products subject to paragraphs (a)(1) through (a)(2)(i), (a)(3) through (a)(4), (a)(6)(i)(A),

¹ These ingredients are nonmonograph except when used to prepare acidulated phosphate fluoride treatment rinses identified in § 355.10(a)(3) of this chapter.

(a)(6)(ii)(A), (a)(7) (except as covered by paragraph (d)(3) of this section), (a)(8)(i), (a)(9) through (a)(10)(iii), (a)(12)(i) through (a)(12)(iv), (a)(14) through (a)(15)(i), and (a)(16) through (a)(18)(i) of this section.

* * * * *
(24) October 7, 1996, for products subject to paragraph (a)(2)(ii) of this section.

4. Part 355 is added to read 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 Packaging conditions.

Subpart C—Labeling

- 355.50 Labeling of anticaries drug products.
- 355.55 Principal display panel of all fluoride rinse drug products.
- 335.60 Professional labeling.

Subpart D—Testing Procedures

- 355.70 Testing procedures for fluoride dentifrice drug products.

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

Subpart A—General Provisions

§ 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 of this chapter.

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

§ 355.3 Definitions.

As used in this part:

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

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

(c) *Anticaries drug.* A drug that aids in the prevention and prophylactic treatment of dental cavities (decay, caries).

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

(e) *Dentifrice*. An abrasive-containing dosage form for delivering an anticaries drug to the teeth.

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

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

(h) *Fluoride supplement*. A special treatment rinse dosage form that is intended to be swallowed, and is promoted to health professionals for use in areas where the water supply contains 0 to 0.7 parts per million (ppm) fluoride ion.

(i) *Preventive treatment gel*. A dosage form for delivering an anticaries drug to the teeth. Preventive treatment gels are formulated in an anhydrous glycerin base with suitable thickening agents included to adjust viscosity. Preventive treatment gels do not contain abrasives.

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

(k) *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.

(l) *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.

(m) *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 when used in the concentration and dosage form established for each ingredient:

(a) *Sodium fluoride*—(1) *Dentifrices containing 850 to 1,150 ppm theoretical total fluorine in a paste dosage form*. Sodium fluoride 0.188 to 0.254 percent with an available fluoride ion concentration ≥ 650 parts per million (ppm).

(2) *Dentifrices containing 850 to 1,150 ppm theoretical total fluorine in a powdered dosage form*. Sodium fluoride

0.188 to 0.254 percent with an available fluoride ion concentration of ≥ 850 ppm for products containing the abrasive sodium bicarbonate and a poured-bulk density of 1.0 to 1.2 grams per milliliter.

(3) *Treatment rinses*. (i) 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.

(ii) An aqueous solution of acidulated phosphate fluoride derived from sodium fluoride acidulated with a mixture of sodium phosphate, dibasic, and phosphoric acid to a pH of 3.5 and which yields an effective fluoride ion concentration of 0.01 percent.

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

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

(v) 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.

(b) *Sodium monofluorophosphate*—(1) *Dentifrices containing 850 to 1,150 ppm theoretical total fluorine in a paste dosage form*. Sodium monofluorophosphate 0.654 to 0.884 percent with an available fluoride ion concentration (consisting of PO_3F^- and F^- combined) ≥ 800 ppm.

(2) *Dentifrices containing 1,500 ppm theoretical total fluorine in a paste dosage form*. Sodium monofluorophosphate 1.153 percent with an available fluoride ion concentration (consisting of PO_3F^- and F^- combined) $\geq 1,275$ ppm.

(c) *Stannous fluoride*—(1) *Dentifrices containing 850 to 1,150 ppm theoretical total fluorine in a paste dosage form*. (i) Stannous fluoride 0.351 to 0.474 percent with an available fluoride ion concentration ≥ 700 ppm for products containing abrasives other than calcium pyrophosphate.

(ii) Stannous fluoride 0.351 to 0.474 percent with an available fluoride ion concentration ≥ 290 ppm for products containing the abrasive calcium pyrophosphate.

(2) *Preventive 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.

(3) *Treatment rinse*. 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.

§ 355.20 Packaging conditions.

(a) *Package size limitation*. Due to the toxicity associated with fluoride active ingredients, the following package size limitations are required for anticaries drug products:

(1) *Dentifrices*. Dentifrice (toothpastes and tooth powders) packages shall not contain more than 276 milligrams (mg) total fluorine per package.

(2) *Preventive treatment gels and treatment rinses*. Preventive treatment gel and treatment rinse packages shall not contain more than 120 mg total fluorine per package.

(3) *Exception*. Package size limitations do not apply to anticaries drug products marketed for professional office use only and labeled in accord with § 355.60.

(b) *Tight container packaging*. To minimize moisture contamination, all fluoride powdered dentifrices shall be packaged in a tight container as defined as a container that protects the contents from contamination by extraneous liquids, solids, or vapors, from loss of the article, and from efflorescence, deliquescence, or evaporation under the ordinary or customary conditions of handling, shipment, storage, and distribution, and is capable of tight reclosure.

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 the following: “anticavity fluoride” (select one of the following as appropriate: “dentifrice,” “toothpaste,” “tooth polish,” “tooth powder;” (optional: “dental”) “preventive treatment gel;” or (optional: “treatment” or “dental”)) (select one of the following: “rinse,” “concentrated solution,” “rinse powder,” or “rinse effervescent tablets”). The word “mouthwash” may be substituted for the word “rinse” in this statement of identity if the product also has a cosmetic use, as defined in section 201(i) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(i)).

(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, describing only the

indication for use that has been established and listed in this paragraph (b), may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

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

(1) *For all fluoride dentifrice (toothpastes and tooth powders) products.* "Keep out of the reach of children under 6 years of age." This warning shall be used in place of the first general warning statement required by § 330.1(g) of this chapter.

(2) *For all fluoride rinse and gel products.* The first general warning statement in § 330.1(g) of this chapter shall be used.

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

(1) *For anticaries dentifrice products—(i) Paste dosage form with a theoretical total fluorine concentration of 850 to 1,150 ppm identified in § 355.10(a)(1), (b)(1), and (c)(1).* Adults and children 2 years of age and older: Brush teeth thoroughly, preferably after each meal or at least twice a day, or as directed by a dentist or doctor. Instruct children under 6 years of age in good brushing and rinsing habits (to minimize swallowing). Supervise children as necessary until capable of using without supervision. Children under 2 years of age: Consult a dentist or doctor.

(ii) *Paste dosage form with a theoretical total fluorine concentration of 1,500 ppm identified in § 355.10(b)(2).* Adults and children 6 years of age and older: Brush teeth thoroughly, preferably after each meal or at least twice a day, or as directed by a dentist or doctor. Instruct children under 12 years of age in good brushing and rinsing habits (to minimize swallowing). Supervise children as necessary until capable of using without supervision. Children under 6 years of age: Do not use unless directed by a dentist or doctor.

(iii) *Powdered dosage form with a theoretical total fluorine concentration of 850 to 1,150 ppm identified in § 355.10(a)(2).* Adults and children 6 years of age and older: Apply powder to a wet toothbrush; completely cover all bristles. Brush for at least 30 seconds. Reapply powder as before and brush

again. Rinse and spit out thoroughly. Brush teeth, preferably after each meal or at least twice a day, or as directed by a dentist or doctor. Instruct children under 12 years of age in good brushing and rinsing habits (to minimize swallowing). Supervise children as necessary until capable of using without supervision. Children under 6 years of age: Do not use unless directed by a dentist or doctor.

(2) *For anticaries treatment rinse products—(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(a)(3)(i), (a)(3)(iv), (a)(3)(v), and (c)(3).* 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. Instruct children under 12 years of age in good rinsing habits (to minimize swallowing). Supervise children as necessary until capable of using without supervision. 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(a)(3)(ii) and (a)(3)(iii).* 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. Instruct children under 12 years of age in good rinsing habits (to minimize swallowing). Supervise children as necessary until capable of using without supervision. Children under 6 years of age: consult a dentist or doctor.

(3) *For stannous fluoride treatment rinse products.* (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 preventive treatment gel products.* 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. Instruct children under 12 years of age in the use of this product

(to minimize swallowing). Supervise children as necessary until capable of using without supervision. Children under 6 years of age: consult a dentist or doctor.

(5) *For all concentrated treatment rinse solutions, powders, and effervescent tablets.* The following statement shall appear as the first statement under directions: "Do not use before mixing with water."

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

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

(2) *For all stannous fluoride treatment rinse, preventive treatment gel, and dentifrice products.* "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 statements—(1) For fluoride treatment rinses and preventive treatment gels.** The following labeling statement may appear in the required boxed area designated "APPROVED USES": "The combined daily use of a fluoride preventive treatment" (select one of the following: "rinse" or "gel") "and a fluoride toothpaste can help reduce the incidence of dental cavities."

(2) *For dentifrice products containing 1,500 ppm theoretical total fluorine.* "Adults and children over 6 years of age may wish to use this extra-strength fluoride dentifrice if they reside in a nonfluoridated area or if they have a greater tendency to develop cavities."

§ 355.55 Principal display panel of all fluoride rinse drug products.

In addition to the statement of identity required in § 355.50, the following statement shall be prominently placed on the principal display panel: "IMPORTANT: Read directions for proper use."

§ 355.60 Professional labeling.

(a) The labeling for anticaries fluoride treatment rinses identified in § 355.10(a)(3) and (c)(3) that are specially formulated so they may be swallowed (fluoride supplements) and are 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 parts per million (ppm)), clean the teeth with a toothpaste and rinse with 5 milliliters (mL) of 0.02 percent or 10 mL of 0.01 percent fluoride ion rinse daily, then swallow. When the water supply contains 0.3 to 0.7 ppm fluoride ion, reduce the dose to 2.5 mL of 0.02 percent or 5 mL of 0.01 percent fluoride ion rinse daily.

(b) The labeling for products marketed to health to health professionals in package sizes larger than those specified in § 355.20 shall include the statements: "For Professional Office Use Only" and "This product is not intended for home or unsupervised consumer use."

Subpart D—Testing Procedures

§ 355.70 Testing procedures for fluoride dentifrice drug products.

(a) A fluoride dentifrice drug product shall meet the biological test requirements for animal caries reduction and one of the following tests: Enamel solubility reduction or fluoride enamel uptake. The testing procedures

for these biological tests are labeled *Biological Testing Procedures for Fluoride Dentifrices*; these testing procedures are on file under Docket No. 80N-0042 in the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857, and are available on request to that office.

(b) The United States Pharmacopeia fluoride dentifrice reference standards along with reference standard stability profiles (total fluoride, available fluoride ion, pH, and specific gravity) required to be used in the biological tests are available to any purchaser upon written request to the United States Pharmacopeial Convention, Inc., 1260 Twinbrook Parkway, Rockville, MD 20852.

(c) Alternative testing procedures may be used. Any proposed modification or alternative testing procedures shall be submitted as a petition in accord with § 10.30 of this chapter. The petition should contain data to support the modification or data demonstrating that an alternative testing procedure provides results of equivalent accuracy.

All information submitted will be subjected to the disclosure rules in part 20 of this chapter.

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

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

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

§ 369.21 [Amended]

5. Section 369.21 *Drugs; warning and caution statements required by regulations* is amended by removing the entries for "SODIUM FLUORIDE DENTIFRICE POWDER" and "SODIUM MONOFLUOROPHOSPHATE DENTIFRICE SOLUTION."

Dated: September 18, 1995.

William K. Hubbard,

Acting Deputy Commissioner for Policy.

[FR Doc. 95-24693 Filed 10-5-95; 8:45 am]

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