DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 355

[Docket No. 80N-0042]

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

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking that amends the tentative final monograph (proposed rule) that would establish conditions under which over-the-counter (OTC) anticaries drug products (drug products that aid in the prevention of dental cavities) are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. This proposal is part of the ongoing review of OTC drug products conducted by FDA. This proposal deals only with matters regarding final formulation testing, i.e., "Laboratory Testing Profiles" (LTP's), for Category I active ingredients in dentifrice formulations, and issues relating to this testing.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by October 13, 1988. Because of the length and complexity of this proposed regulation, the agency is allowing a period of 120 days for comments and objections instead of the normal 60 days. New data by June 15, 1989. Comments on the new data by August 15, 1989. Written comments on the agency's economic impact determination by October 13, 1988.

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

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

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

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information. In response to the advance notice of proposed rulemaking, the Panel Chairman, 4 drug manufacturers' associations, 10 drug manufacturers, 1 consumer, 7 health care professionals, 2 health care professional societies, and 1 coalition opposed to fluoridation submitted comments. Copies of the comments received are on public display in the Dockets Management Branch.

The agency stated in the advance notice of proposed rulemaking that the Panel's recommended LTP's represent a new concept with many technical issues yet to be resolved; therefore, they were not included as part of the proposed monograph in the first segment of the tentative final monograph published in the **Federal Register** on September 30, 1985 (50 FR 39854). The agency stated therein that the tentative final monograph for OTC anticaries drug products would be issued in two segments. The first segment contains the agency's responses to general comments on anticaries drug products, comments on the switch of prescription anticaries drug products to OTC status, comments on specific anticaries active ingredients, comments on dosages for anticaries active ingredients, and comments on the labeling of anticaries drug products. This second segment, which is an amendment to the proposed rule for OTC anticaries drug products, contains the agency's proposals regarding LTP's for Category I active ingredients in dentifrice formulations, and issues relating to this testing. The agency held an open public meeting on September 26 and 27, 1983, regarding unresolved technical issues concerning the LTP's and reopened the administrative record to include the proceedings of the public meeting and to allow comment on matters raised at the meeting (48 FR 38853). In a notice published in the **Federal Register** of October 25, 1983 (48 FR 49304), the agency advised that the administrative record for OTC anticaries drug products would remain open until December 2, 1983, to allow for consideration of data and information that had been filed in the Dockets Management Branch concerning matters raised at the meeting. Data and information received after the administrative record was reopened are on public display in the Dockets Management Branch.

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

The previously published tentative final monograph (50 FR 39854) and this amendment constitute FDA's tentative adoption of the Panel's conclusions and recommendations on OTC anticaries drug products, as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them.

The OTC procedural regulations (21 CFR 330.10) now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking

process before the establishment of a final monograph. Accordingly, FDA will no longer use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but will use instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

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

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

I. The Agency's Tentative Conclusions on the Comments

A. General Comments on Anticaries Drug Products

1. Three comments addressed the importance of the availability of the fluoride ion in establishing the effectiveness of OTC anticaries dentifrices. One comment stated that the Panel recognized this importance and established assays to show that the availability of the fluoride ion is ultimately responsible for the cariostatic effect in anticaries dentifrices, and that the source of the fluoride ion was not an issue in the Panel's deliberations. A second comment acknowledged the importance of the availability of the fluoride ion, but felt that only one concentration of the soluble fluoride ion should be specified in the Panel's tables for each active fluoride compound rather than values for both a freshly-prepared paste and an aged paste. The comment was opposed to the LTP parameters, which it believed imposed arbitrary standards not correlated with clinical data and required the establishment of reference standards. The comment claimed that no one has presented results from the three biological tests in the LTP's that can be correlated with clinical effectiveness. Further, the comment stated that the specification of a minimum available fluoride-compound concentration and an analytical procedure for determining this concentration suffice to ensure an effective anticaries dentifrice.

The third comment agreed that the fluoride ion is solely responsible for the effectiveness of an anticaries dentifrice, but was concerned about the exclusion of organic fluoride compounds as a source of the fluoride ion. The comment did not provide the specific names of any organic fluoride-containing compounds or any data to show that these compounds are safe and effective as anticaries agents. The comment claimed that the Panel was only interested in measuring the amount of available fluoride ion and not the source of the fluoride ion. The comment noted that the Panel did not review any data on organic fluorides because there were none on the United States market at the time of its deliberations. The comment stated that "bioequivalence and bioavailability are the critical factors in determining if the fluoride ion is safe and effective, not the organic or inorganic 'source' of the fluoride ion." The comment suggested that the scientific definition of fluoride should be described as the anion, irrespective of the inorganic or organic source of the fluoride ion. The comment did not submit any data to support its claim of the bioavailability of fluoride ions from an organic fluoride compound.

The agency agrees with the comments that the availability of the fluoride ion in concentrations which are safe and effective is the most important consideration in any fluoride-containing dentifrice. The Panel recognized the significance of the fluoride ion in preventing dental caries and discussed the use of inorganic fluorides in dental products at 45 FR 20675. The Panel was concerned about the bioavailability of the fluoride ion, especially in dental formulations with new abrasives. One of the major problems with fluoride-containing dentifrices is the possible incompatibility of the fluoride ion with the abrasive. Some abrasives may combine with the fluoride ion and decrease its availability to the teeth.

To underscore the importance that the Panel placed on the availability of the fluoride ion, the first analytical test value listed in the LTP tables refers to the concentration of soluble fluoride ion required for each fluoride compound used in dental formulations. The Panel developed LTP's as a way of predicting which dental formulations will be effective without the need for expensive, long-term clinical trials. The test values in the LTP tables were based on certain analytical tests that were obtained from dentifrice formulations that had been proven to be effective through clinical testing. In addition, the bioavailability of the fluoride ion also had been established in biological tests to ensure comparability with the results of clinical testing. The agency concurs with the Panel's recommendation regarding the need for information concerning the availability of the fluoride ion in anticaries dentifrices. Therefore, the agency is proposing to include in the active ingredient section of this tentative final monograph the amount of required available fluoride ion for each Category I fluoride active ingredient in a dentifrice formulation and to require that fluoride dentifrice drug products meet the test requirements of any two of the biological tests set forth by the Panel. (See comments 4 and 7 below.) The agency believes that requirements for parameters other than available fluoride ion and the biological testing, such as specific gravity and pH, are adequately addressed in the current good manufacturing practice for finished pharmaceuticals (21 CFR Part 211) and need not be specifically addressed in the monograph. (See comment 4 below.)

In the LTP tables proposed by the Panel, the soluble fluoride ion values were given for both the fresh and the aged formulation because the Panel believed that the concentration of free fluoride ion will change as the dentifrice ages. The aging time period was different for each of the fluoride-containing compounds and this resulted in different values for free fluoride ion for each of the compounds. The values

in the LTP tables represented the lowest measured values for aged dentifrices that were actually used and found to be effective in clinical trials. However, in its report the Panel did not discuss the amount of time that these dentifrices had aged when the lowest fluoride ion values were measured and did not include in the tables the actual age of the dentifrice at the time the listed "aged minimal" soluble fluoride ion concentration was determined. Because the Panel did not specify the age of the dentifrices at which the soluble fluoride ion values for the dentifrices must meet or exceed the "aged minimal F values" listed in the LTP tables, these values cannot be used to determine if a dentifrice is Category I, safe and effective. However, the agency and manufacturers can use these minimal soluble fluoride ion values to determine expiration dating for fluoride dentifrices that will be covered by the final monograph. (See comment 17 below.)

The agency does not accept one comment's view that only the bioavailability of the fluoride ion, and not the source, is important in determining the effectiveness of a fluoride-containing dentifrice. The inorganic fluorides that are specified in the tentative final monograph have been reviewed by the Panel, and the critical values for soluble fluoride ion for each compound have been established. These values were obtained from an extensive amount of testing, including laboratory, animal, and clinical tests. In order for a fluoride compound other than those listed in the final monograph to be approved for use in a dentifrice, similar data would be required. As stated by the Panel at 45 FR 20677, "If a manufacturer wishes to use an untested chemical compound as a fluoride source, he or she must file to obtain an approved NDA (new drug application) in accordance with FDA's new drug regulations." An alternative procedure is to petition the agency to amend the monograph to include specific organic fluorides as active ingredients for use in dental formulations. With either procedure, the manufacturer must submit data showing the organic fluoride to be safe and effective for its intended use.

2. One comment requested that the allowable upper limit of fluoride concentration in a dentifrice be increased to 1,500 parts per million (ppm). The comment stated that the first fluoride dentifrices on the OTC market contained the minimally effective dosage and that it is time to change the focus toward an optimal, not minimal, concentration. The comment added that dentifrices containing 1,500 ppm fluoride have been advocated in the dental literature and have been widely used in Europe for a number of years without any safety problems. The comment stated that, based on studies cited by the Panel (45 FR 20673), if the amount of fluoride in a dentifrice is 1,500 ppm, then the amount of dentifrice swallowed per average brushing would be 0.36 milligram (mg) or less. The comment contended that this amount is not only safe from a standpoint of enamel mottling, but it is suboptimal from a standpoint of caries prevention because the optimal fluoride intake is no less than 0.50 mg for infants and 1 mg for older children.

When the Panel reviewed fluoride dentifrices, most of the products on the market contained theoretical total fluorine at concentrations between 900 and 1,100 ppm. Based on the submitted data, these products were shown to be safe and effective. Since that time, several comments submitted additional data that are sufficient to expand the theoretical total fluorine concentration range to 850 to 1,150 ppm. (See comments 5 and 6 below.)

While the comment's statement regarding the safety of a dentifrice containing 1,500 ppm theoretical total fluorine is correct, no evidence has been provided in the administrative record to show an added benefit to persons who use a dentifrice containing 1,500 ppm theoretical total fluorine as compared to formulations containing 1,150 ppm theoretical total fluorine. The agency has approved under a new drug application (Ref. 1) the OTC marketing of a fluoride dentifrice containing 1,500 ppm theoretical total fluorine. However, these data are not in the public domain. General recognition of the effectiveness of a drug must be based on adequate published or publicly available medical and scientific data. (*United States v. 41 Cases * * * Naremco*, 420 F.2d 1126 (C.A. 5, 1970); *United States v. An Article of Drug * * * Mykocert*, 345 F. Supp. 571 (D.C. 1972); *United States v. An Article of Drug * * * Asper Sleep*, CCH F.D. and Cosm. L. Rep. 40,821 Civil No. 70–C–196 (N.D. Ill. 1971); *United States v. An Article of Drug * * * Furestrol Vaginal Suppositories*, 294 F. Supp. 1307 (N.D. Ga. 1968).) Therefore, even though a dentifrice containing 1,500 ppm fluoride has been shown, on the basis of proprietary information, to be safe and effective as required by 21 U.S.C. 355(d), there is not adequate information in the administrative record for this rulemaking at this time to demonstrate that such a dentifrice is generally recognized as effective. Because the agency is unable to make a determination at this time that a dentifrice containing more than 1,150 ppm fluoride is generally recognized as safe and effective as an OTC anticaries drug product, FDA is proposing that such products be Category III. Category III status at the tentative final stage of this rulemaking or nonmonograph status at the final stage of this rulemaking would not affect the legal OTC marketing of this drug under an approved application.

At present, a dentifrice containing 1,500 ppm fluoride cannot be lawfully marketed as an OTC anticaries drug product in the absence of an approved application. However, the agency would consider extending the upper limit of acceptable values in the monograph if sufficient data are submitted to the public record demonstrating an added benefit from using a dentifrice with concentrations higher than 1,150 ppm theoretical total fluorine without an increase in risks (safety) to consumers.

Reference

(1) Copy of FDA-approved labeling from NDA 19–518, OTC Volume 08LTPTFM, Docket No. 80N–0042, Dockets Management Branch.

3. One comment from a manufacturers' association recognized the possibility that an inactive ingredient that is not currently contained in marketed fluoride dentifrices might be added to a formulation in the future. The comment recommended that the requirements for new fluoride dentifrices formulations be qualified with the statement "* * * if any ingredient that is known or suspected of interfering with fluoride activity is present in a formulation, appropriate effectiveness testing in addition to the analytical tests included in the profile tables must be conducted."

A comment from a manufacturer agreed with the comment above and stated that an ingredient in a dentifrice could counteract the anticaries effect of the fluoride, even though the product still met the LTP testing standards. As an example, the comment stated that certain soluble materials, such as some of the phosphonates, are known to retard the rate of posteruptive mineralization of the teeth. The comment noted, however, that "mineralization-retarding" ingredients have been used in research investigations and are known to be present in at least one dentifrice sold outside the United States. The comment stated further that it is possible to add enough "retarding agent" to a fluoride dentifrice formulation to reduce the

anticaries effect of such a formulation to zero (as measured by animal caries testing) without affecting the concentration of the fluoride ion as measured in analytical tests.

The comment concluded that the effectiveness of a fluoride dentifrice formulation containing a "retarding agent" could not be adequately assessed by any set of tests that did not include at least an animal caries test and suggested that a human caries test might be required to adequately assess the anticaries effectiveness of such a formulation. The comment also suggested that manufacturers who use an ingredient that is known or suspected to counteract the anticaries effectiveness of the fluoride in a dentifrice should verify the effectiveness of the product by appropriate animal testing or, preferably, clinical testing.

Another comment suggested that fluoride dentifrices that contain those fluoride ingredients listed in the monograph, with "minor formulation changes," be considered "old" drugs if the manufacturer can show that the "old" fluoride ingredient is bioavailable in concentrations sufficient to demonstrate safety and effectiveness. "New" aspects of such drug products would be those aspects that dramatically change the "old formulations." If aspects of the product are "new," only the "new" aspects of the product should be evaluated under the new drug application process, while simultaneously allowing "old" drug issues to be resolved under the monograph. The comment contended that the agency would thus avoid lengthy drug approval problems inherent in 3-year massive clinical studies that merely demonstrate that fluoride is an effective anticaries agent.

The Panel recommended that Category I fluoride ingredient/abrasive combinations in dentifrice formulations that were not specifically reviewed by the Panel be required to contain an amount of available fluoride ion equal to or greater than the highest available fluoride ion value recommended for the specific fluoride ingredient (45 FR 20677). The agency believes that such standards for Category I fluoride ingredient/abrasive combinations in dentifrice formulations are applicable to all new dentifrice formulations that contain Category I fluoride ingredients specified in the monograph (see comment 11 below), including formulations that contain inactive ingredients that are not currently present in marketed fluoride dentifrices. It is therefore unnecessary to address some "new" aspects of such dentifrices under the new drug procedures as suggested by one comment. In addition, regulations in 21 CFR 330.1(e) concerning inactive ingredients, which state that a product may contain only suitable inactive ingredients which do not interfere with the effectiveness of a product or with suitable tests or assays for the product, adequately address concerns raised by two comments that some inactive ingredients may interfere with the fluoride activity in the formulation.

Also, regulations concerning laboratory controls in 21 CFR 211.160(b) require that "laboratory controls shall include the establishment of scientifically sound and appropriate * * * test procedures designed to assure that * * * drug products conform to appropriate standards of identity, strength, quality, and purity." Therefore, manufacturers are responsible for using appropriate test procedures for fluoride dentifrices under this regulation. In its LTP's, the Panel considered an animal caries test as one of the appropriate tests for determining the bioavailability of fluoride ion in Category I fluoride dentifrice formulations, and the agency has included this test in the proposed monograph. If an animal caries test is the appropriate test to demonstrate the possible inhibition of the fluoride ion in a dentifrice formulation containing an inactive ingredient not present in currently marketed fluoride dentifrices, as one comment suggested, then manufacturers are required to use such a test under the proposed monograph and § 211.160(b). Consequently, it is unnecessary to add a specific statement concerning such inactive ingredients in the monograph. In addition, the agency does not believe that clinical testing is necessary for Category I fluoride/abrasive dentifrice formulations that were not specifically reviewed by the Panel. (See comment 11 below.)

B. Comments on Testing Guidelines

4. Several comments objected to the agency's decision not to include the Panel's recommended LTP's for Category I fluoride dentifrices in the anticaries monograph. The comments stated that the dental profession and the industry accept the concept of establishing the effectiveness of the fluoride dentifrices specified in the panel's LTP tables (45 FR 20679 to 20681) by requiring that they meet laboratory testing standards, i.e., LTP's, rather than requiring that they meet lengthy, expensive clinical testing standards. Several comments stated that the concept of using LTP's to establish the effectiveness of fluoride dentifrices is supported by substantial scientific data that show a strong correlation between the efficacy values obtained from clinical testing and those values obtained from specific laboratory tests (LTP's) on dentifrices. Several comments emphasized that the anticaries effectiveness of fluoride dentifrices is dependent on the chemical availability and the bioavailability of the fluoride ion in the dentifrice formulation. They further explained that these availability parameters are adequately measured by chemical and biological testing, obviating the need to perform clinical testing to establish the effectiveness of the fluoride dentifrices that are included in the Panel's LTP tables.

One comment suggested that products containing the same fluoride compound and abrasive combinations as those included in the Panel's recommended LTP tables be required to meet the chemical test requirements, but not the biological test requirements recommended by the Panel. This comment suggested that fluoride/abrasive combinations that are listed in the Panel's LTP tables meet the following requirements:

(1) Theoretical total fluorine concentration between 850 and 1,150 ppm, and

(2) Specific gravity within the range 1.1 to 1.7, and

(3) A fresh soluble fluoride concentration at least as great as the table value for the particular fluoride/abrasive combination, and

(4) An aged minimal soluble fluoride concentration at least as great as the table value for that particular fluoride/abrasive combination, and

(5) A pH value within the range listed in the table for that particular fluoride/abrasive combination;

or

(1) and (2) above, and

(6) Demonstrate through appropriate clinical trials that the formulation is effective.

As stated in the advance notice of proposed rulemaking (45 FR 20666), the agency's intent in excluding the Panel's recommended LTP's from the monograph in that document was to resolve several questions regarding the use of the LTP's in regulating abrasive-containing fluoride dentifrices. The Panel's final formulation testing recommendations represented a new concept for regulating drugs under an OTC drug monograph.

The Panel recognized that the active moiety in abrasive-containing fluoride dentifrices is available fluoride ion and was aware of the problems that can

occur when the abrasive in such dentifrices interacts with the fluoride ion, reducing the amount of available fluoride ion with a concomitant reduction in the effectiveness of the product to prevent caries. With the assistance of members of the drug industry, the Panel developed LTP's for fluoride dentifrices that it believed correlate with the results of clinical testing. These LTP's do not require human testing. The LTP's were formulated by the Panel after reviewing industry submitted laboratory testing results on actual lots of several different types of fluoride dentifrices that had been clinically tested and found effective. The Panel used the actual test values for these clinically effective lots of fluoride dentifrices to develop the LTP's.

The Panel recommended that a fluoride dentifrice product that contains a Category I fluoride ingredient/abrasive combination that is listed in the tables in its report could be marketed if it meets or exceeds the soluble fluoride ion levels listed in the tables in addition to meeting other parameters set by the Panel such as limits for specific gravity and pH, and biological testing standards (45 FR 20677 to 20681). Combinations of Category I ingredients and abrasives that are not listed in the tables in the report are discussed in comment 11 below.

After reviewing the comments submitted in response to the Panel's report, the agency concluded that there were still several unresolved questions concerning the LTP's. In an effort to resolve these questions, the agency announced a public meeting to discuss appropriate LTP's for OTC abrasive-containing fluoride dentifrices in the **Federal Register** of August 26, 1983 (48 FR 38853). Specific agency questions concerning the LTP's were posed in that meeting announcement. The public meeting was held September 26 and 27, 1983. Items discussed at the meeting included the addition of new testing technology, such as remineralization testing for fluoride dentifrices, to the LTP requirements. Also discussed were mechanisms for adding updated specific LTP test methods to those testing methods that were reviewed by the Panel and that are on file in the anticaries drug products rulemaking administrative record in the Dockets Management Branch (Ref. 1). Whether or not specific test methods should be required to obtain LTP test values for fluoride dentifrices was discussed, in addition to the importance of including test parameters such as specific gravity, pH, and stannous ion content in agency requirements for fluoride dentifrices. Participants in the meeting provided a great deal of information regarding the agency's concerns and questions about the LTP's (Refs. 2 and 3). There was general agreement that new testing technology has been developed for fluoride dentifrices since the Panel's review of these dentifrices and that new testing technology continues to evolve. There was a consensus that, although the testing methods reviewed by the Panel are valid techniques, the agency's requirements for testing fluoride dentifrices should not preclude the application of new, advanced technology in testing fluoride dentifrices, nor should the agency require specific test methods to obtain LTP test values for fluoride dentifrices. Most meeting participants agreed that parameters, such as specific gravity, pH, and stannous ion content, specified by the Panel in the LTP tables were based on particular fluoride dentifrice formulations that were in the marketplace during the Panel's deliberations. However, these parameters do not necessarily reflect appropriate test limits for currently marketed fluoride dentifrice formulations that are different from the previous formulations reviewed by the Panel. The majority of the participants believed that these formulation specific parameters have an important impact on the availability of the fluoride ion in a particular fluoride dentifrice formulation. However, these parameters vary from one formulation to another and the most important testing criterion for predicting the effectiveness of a fluoride dentifrice is the availability of the fluoride ion in the formulation.

The agency has carefully reviewed the Panel's recommendations concerning the LTP's, the comments concerning the LTP's, and the information provided during the September 1983 meeting. Prior to the Panel's recommendations, the only accepted methods of assuring the effectiveness of fluoride dentifrice formulations were clinical trials. Such clinical trials are long-term studies that require large numbers of children, the population most vulnerable to caries; are expensive; and require a high level of expertise in employing appropriate criteria to produce conclusive results. The Panel was aware of the problems involved in such extensive clinical trials but was also concerned that the abrasive in the dentifrice could alter the availability of the fluoride ion and therefore the effectiveness of fluoride dentifrices. The Panel sought an alternative to clinical trials that would still ensure the effectiveness of fluoride dentifrices and recommended that fluoride dentifrices meet laboratory testing standards, i.e., LTP's , in lieu of the long, expensive clinical trials.

As one former Panel member stated in his comments to the advance notice of proposed rulemaking, it is clearly not in the best interest of consumers or industry to require additional clinical testing of Category I active ingredients because of formulation changes that can be demonstrated in the laboratory to be inconsequential and not to interfere with the effectiveness of the dentifrices (Ref. 4). The agency agrees with the comments and the Panel that the requirement of lengthy clinical trials is no longer warranted and that appropriate laboratory testing is adequate to assure the effectiveness of fluoride dentifrices containing Category I active ingredients. Therefore, the agency is accepting the Panel's recommendation that fluoride dentifrices meet or exceed the soluble fluoride ion level specified for each particular fluoride ingredient listed in the monograph and meet the test requirements of any two of the following biological tests: (1) Enamel solubility reduction, (2) fluoride uptake by enamel, and/or (3) animal caries reduction. The agency is including these requirements in the monograph.

The Panel's major concern was to assure the availability of fluoride ion in abrasive-containing dentifrices. Based on the fluoride ion values recommended in the Panel's LTP's and in comments submitted in response to the Panel's recommendations (see comment 5 below), the agency is proposing to include in the active ingredient section of the monograph the amount of available fluoride ion required for each Category I fluoride active ingredient in a dentifrice dosage form. As discussed in comment 6 below, the agency is also proposing ranges of concentrations for fluoride ingredients in the monograph that correspond to a range of 850 to 1,150 ppm theoretical total fluorine. In addition, the agency is proposing to include the Panel's recommendations concerning biological test requirements for fluoride dentifrices (45 FR 20677 and 20678) in the monograph. (See comment 7 below.) Thus, the active ingredient list in § 355.10(a) for dentifrices is being amended as follows:

(a) *Dentifrices.* (1) Sodium fluoride 0.188 to 0.254 percent with an available fluoride ion concentration>650 parts per million.

(2) Sodium monofluorophosphate 0.654 to 0.884 percent with an available fluoride ion concentration (consisting of

$PO_3F^=$ and F^- combined)≥800 parts per million.

(3) Stannous fluoride 0.351 to 0.474 percent with an available fluoride ion concentration≥700 parts per million for products containing abrasives other than calcium pyrophosphate.

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

The agency is also adding new Subpart D to Part 355 concerning biological testing requirements to read as follows:

Section 355.70 Testing Procedures for Fluoride Dentifrice Drug Products.

A fluoride dentifrice drug product must meet the test requirements of any two of the following biological tests: Enamel solubility reduction, fluoride uptake by enamel, and/or animal caries reduction. The testing procedures for these biological tests are on file under Docket No. 80N–0042 in the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, labeled *Biological Testing Procedures for Fluoride Dentifrices,* and are available on request to that office. Alternative testing procedures may be used. Any proposed modification or alternative testing procedures shall be submitted as a petition under the rules established in § 10.30. 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 subject to the disclosure rules in Part 20 of this chapter.

As with all products covered by OTC drug monographs, it is the responsibility of the manufacturer to assure that its products meet the standards set forth in the appropriate monograph. In the case of fluoride dentifrices, the agency is proposing that manufacturers ensure that their products contain the amount of available fluoride ion and meet the biological testing requirements set forth in the monograph for OTC anticaries drug products.

The agency believes that the Panel's recommended requirements in the LTP tables for parameters other than available fluoride ion and biological test requirements such as specific gravity and pH, that relate to inactive ingredients and appropriate manufacturing procedures, are adequately addressed in the current good manufacturing practice regulations (21 CFR Part 211) and need not be specifically addressed in the monograph. For example, § 211.160(b) states

> Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity.

In addition, § 211.165 states in part that "For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release,"; that "The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels,"; and that "The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented." In addition, by regulation (21 CFR 330.1(e)) a product may contain only suitable inactive ingredients which are safe and do not interfere with the effectiveness of the preparation or with suitable tests or assays to determine if the product meets its professed standards of identity, strength, quality, and purity. In conclusion, the agency offers the Panel's recommended testing requirements, as set forth in the LTP tables (45 FR 20679 to 20681) and revised in comments 5 and 6 below, as appropriate testing limits for parameters such as specific gravity, pH, and stannous ion content, but does not find it necessary to include them in a final monograph.

References

(1) OTC Volume 080248.

(2) Minutes of a Public Meeting to Address Laboratory Testing Profiles for OTC Abrasive-Containing Fluoride Anticaries Drug Products, September 26 and 27, 1983, Docket No. 80N–0042, Dockets Management Branch.

(3) Transcripts of a Public Meeting to Address Laboratory Testing Profiles for OTC Abrasive-Containing Fluoride Anticaries Drug Products, September 26 and 27, 1983, Docket No. 80N–0042, Dockets Management Branch.

(4) Comment No. C00001, Docket No. 80N–0042, Dockets Management Branch.

5. One comment from a manufacturers' association noted that the Panel's recommended LTP tables (45 FR 20679 to 20681) are based entirely on data generated by industry and submitted to the Panel. The comment requested that corrections of errors resulting from either misinterpretations of the data submitted by industry or mistranscriptions of the numbers submitted by industry be made as follows: (1) In Table 1 for sodium fluoride dentifrices (45 FR 20679), the test dilutions for both the "Soluble Fluoride Ion" and the "Hydrogen Ion Concentration (pH)" should be 1:3 rather than 1:10; (2) in Table 2 for sodium monofluorophosphate dentifrices (45 FR 20680) under "II. Hydrogen Ion Concentration (pH)," the pH range listed for the abrasive alumina should be 6.4 to 9.0 rather than 5.0 to 9.0 and the pH range listed for the abrasive dicalcium phosphate should be 6.3 to 7.6 rather than 6.5 to 7.8; (3) in Table 3 for stannous fluoride dentifrices (45 FR 20681) under "I. Soluble Fluoride Ion," the test values for fluoride ion listed for the abrasives, insoluble sodium metaphosphate, silica, and others should be 700 ppm for the fresh value and 650 ppm for the aged minimal value, rather than 600 ppm for the fresh value and 500 ppm for the aged minimal value; (4) in Table 3 for stannous fluoride dentifrices (45 FR 20681) under "II. Soluble Stannous Ion," the test dilution for the abrasive calcium pyrophosphate should be 1:3 rather than 1:10; and (5) in Table 3 for stannous fluoride dentifrices (45 FR 20681) under "III. Hydrogen Ion Concentration (pH)," the test dilution for the abrasive calcium pyrophosphate should be 1:3 rather than 1:10 and the test dilution for the abrasives insoluble metaphosphate, silica, and others should be 1:4 rather than 1:10.

Another comment from a manufacturer that provided test data to the Panel stated that the allowable maximum dilution factor of 1:10 weight per weight (w/w) is inappropriate for some dentifrices listed in the LTP tables because the minimum soluble fluoride levels had been actually determined by the manufacturer using a dilution factor of 1:3 (w/w). The comment further stated that as the dilution factor becomes larger, more fluoride ion is likely to become soluble. Therefore, a larger dilution factor (1:10) may give a false, higher measured soluble fluoride ion concentration than a lower dilution factor (1:3) for a particular dentifrice sample. For example, a 1:3 dilution of a sodium fluoride plus high-beta-phase calcium pyrophosphate toothpaste might yield a low unacceptable measured level of soluble fluoride ion of 500 ppm (below an acceptable 648 ppm) for a fresh product, whereas the same product at a 1:10 dilution might well yield an acceptable measured level of soluble fluoride ion of ≥648 ppm. Thus, there is a risk that the batch of product found acceptable when measured at a 1:10 dilution may not be as effective as dentifrices that have been found to be

clinically effective. Another comment recommended that the changes above requested by the manufacturer and the manufacturers' association be incorporated into the LTP tables.

A fourth comment from a manufacturers' association recommended that in Table 2 for sodium monofluorophosphate dentifrices (45 FR 20680) under "II. Hydrogen Ion Concentration (pH)," the list of specific pH ranges for specific abrasives be replaced by an expanded pH range of 4.2 to 10.0 that is applicable to all abrasives. This comment also requested that the Panel's recommended heading "Maximum test dilution" in Tables I and III be changed to read "Test dilution" and that values in this column be 1:3 and not 1:10 because the test values are actual test values that were determined at a dilution of 1:3 and not theoretical test values.

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 that appear in the advance notice of proposed rulemaking (45 FR 20679 to 20681) and finds them appropriate. In addition, the agency agrees with the one comment that the term "test dilution" is preferable to the term "maximum test dilution" because "test dilution" more accurately indicates the precise dilution factor used.

With respect to one comment's request that the pH ranges specified for particular abrasives listed in Table 2 be replaced by a general expanded pH range of 4.2 to 10 for all abrasives, the agency believes that it is unnecessary to change the Panel's Table 2 because it provides specific pH guidelines for particular fluoride dentifrice formulations that were reviewed by the Panel. The Panel specified the pH ranges for particular abrasives in fluoride dentifrices in the LTP tables because pH has an important role in determining the availability of the fluoride ion in the specific formulations that the Panel reviewed. The agency agrees with the manufacturers' association that an expanded pH range of 4.2 to 10 would apply to all abrasives, but, as explained above, it is not necessary to revise the list of specific pH ranges for specific abrasives in Table 2 (45 FR 20680) because these specific pH ranges provide valid information concerning appropriate pH ranges for the particular fluoride dentifrices that were reviewed by the Panel. Although the agency is not revising the Panel's LTP tables to include a general expanded pH range of 4.2 to 10, this does not preclude the acceptability of a fluoride dentifrice formulation with a pH different from that specified by the Panel, provided that the dentifrice is safe, meets the levels of available fluoride ion and the biological testing requirements identified in the final monograph, and meets scientifically sound and appropriate specifications, standards, and test procedures to ensure that the product conforms to appropriate standards under FDA's current good manufacturing practice regulations (21 CFR Part 211). (See comments 4 above and 11 below.)

6. Several comments requested that the agency widen the Panel's recommended acceptable range of specific gravity values for fluoride dentifrices from 1.3 to 1.7 to a range of 1.1 to 1.7 to accommodate new abrasive systems that are based on silica, an abrasive that is less dense than the older phosphate and calcium carbonate abrasives. The comments stated that, because the abrasive is the major inactive and most dense ingredient in dentifrices, the density of the abrasive has a significant impact on the specific gravity of the dentifrice formulation. Fluoride dentifrices with less dense silica abrasive systems have lower specific gravities than fluoride dentifrices with more dense phosphate or calcium carbonate abrasive systems. One comment explained that silica abrasives are more efficient than phosphate abrasives in cleaning the teeth, i.e., less silica abrasive is needed to produce the same cleaning effect that a larger amount of phosphate abrasive produces, and, as a result, silica abrasives are used in dentifrices at roughly half the weight percent as phosphate abrasives. Another comment noted that the Panel offered no analysis or justification for its recommendation that the specific gravity of all fluoride dentifrices be between 1.3 and 1.7 and apparently it based this recommendation solely on the values for the particular dentifrice formulations that it reviewed.

One comment from a manufacturer requested a specific mathematical adjustment of the Panel's recommended range of allowed total fluorine level (900 ppm to 1,100 ppm) to 1,140 ppm for its particular fluoride dentifrice product to accommodate a change in the specific gravity of the product. The comment explained that a change in the formulation of its fluoride dentifrice from a calcium pyrophosphate abrasive (old product) to a silica abrasive (new product) reduces the specific gravity from 1.56 for the old product to 1.37 for the new product. The comment contended that consumers dispense dentifrices onto a toothbrush by volume, not by weight, and thus the same volume of new product would deliver a lower amount of theoretical total fluorine by weight than the old product because of the lower specific gravity of the new abrasive. For example, if 1 gram (g) of the old product with a specific gravity of 1.56 is dispensed on a toothbrush, it will contain 1 mg theoretical total fluorine. However, if 1 g of the new product with the lower specific gravity of 1.37 is dispensed on a toothbrush, it will only contain 0.88 mg theoretical total fluorine. The comment explained that the Panel's recommended range of 900 to 1,100 ppm theoretical total fluorine content does not allow for the addition of an amount of total fluoride compound large enough to produce a product that provides an equal amount of theoretical total fluorine in an equal volume of fluoride dentifrice formulation as was contained in the old calcium pyrophosphate dentifrice. The comment requested that a correction factor (i.e., the old dentifrice specific gravity value divided by the new dentifrice specific gravity value and multiplied by 1,000 to yield a concentration of theoretical total fluorine in ppm) be allowed for its new silica dentifrice to enable the same amount of total fluorine per volume to be delivered on a toothbrush as would be delivered by volume for the old formulation. Alternatively, the comment requested that the range of 900 to 1,100 ppm for theoretical total fluorine be widened to 850 to 1,150 ppm to cover the practical range of specific gravity. In addition, the comment expressed concern that the final rulemaking would require only a single level of fluoride concentration for fluoride dentifrices as set forth in § 355.10 of the Panel's recommended monograph (45 FR 20690). The comment believed that specifying only single fluoride levels in the monograph could lead to the interpretation that the Panel's recommended fluoride level range of 900 to 1,100 ppm is an allowable tolerance for quality control variation rather than an allowable fluoride level range to compensate for variations in specific gravity. Another comment from a manufacturers' association listed the theoretical total fluorine concentration range of 850 to 1,150 ppm as an appropriate parameter for fluoride dentifrices without specifically commenting on the difference between this range and the Panel's range of 900 to 1,100 ppm for theoretioal total fluorine.

Two comments contended that specific gravity is not an important parameter in determining the anticaries effectiveness of fluoride dentifrices. One of these comments submitted three published clinical studies that compare the anticaries effectiveness of fluoride dentifrice formulations with the same fluoride compounds, but different abrasive systems (Refs. 1, 2, and 3). Two of the studies compare 0.4 percent stannous fluoride dentifrices containing phosphate or silica abrasives (Refs. 1 and 2). The third study compares 0.76 percent sodium monofluorophosphate dentifrices containing phosphate or silica abrasives (Ref. 3). The studies do not discuss differences in the specific gravity of the dentifrices studied. All three studies concluded that the effectiveness of the silica-abrasive dentifrices is comparable to the effectiveness of the phosphate-abrasive dentifrices. The comment argued that differences in the specific gravity of the dentifrices tested in the three studies did not result in significant differences in the anticaries effectiveness of the dentifrices. The comment concluded, based on the three studies, that specific gravity is not an important test parameter for fluoride dentifrices and that, because specific gravity does not affect dentifrice efficacy, there is no reason to adjust individual dentifrice formulations to compensate for specific gravity variability. The comment added that the current limits of fluoride concentration have been used, unadjusted, for more than 20 years throughout a series of formulation changes. The comment expressed concern that if FDA were to conclude in one instance that the fluoride concentration in one fluoride dentifrice formulation should be adjusted to compensate for a specific gravity variation, the necessity of adjusting fluoride levels in all dentifrices could be imposed on manufacturers.

The Panel based its recommendations concerning appropriate ranges for the parameters of theoretical total fluorine and specific gravity for fluoride dentifrices on its review of specific dentifrice formulations submitted to it and did not consider the possibility that the use of new, less dense abrasives in effective fluoride dentifrice formulations could lower the specific gravity of the formulation below 1.3 without compromising the anticaries effectiveness of the dentifrice. The Panel recommended an allowable theoretical total fluorine range of 900 to 1,100 ppm and a specific gravity range of 1.3 to 1.7 for fluoride dentifrices (45 FR 20677).

The agency agrees with the comments that the Panel's recommended range of 900 to 1,100 ppm for theoretical total fluorine can be widened to 850 to 1,150 ppm because the most important parameter in determining the effectiveness of such dentifrices is the amount of available fluoride ion content rather than theoretical total fluorine content. The agency is specifically including requirements for the available fluoride ion content of fluoride dentifrices in the tentative final monograph. (See comment 4 above.) Therefore, the agency believes that 850 to 1,150 ppm is an appropriate range for theoretical total fluorine that will accommodate the newer less dense abrasive systems without compromising the effectiveness of fluoride dentifrices.

In response to one comment's concern that adjustments in the theoretical total fluorine levels might be required to compensate for variability in the specific gravity of different fluoride dentifrice formulations, the agency does not intend to require such adjustments. In response to another comment's concern regarding the intent of the fluoride ingredient concentrations specified in the monograph and the intent of the allowable theoretical total fluorine range of 850 to 1,150 ppm, this range is intended to allow a range of theoretical total fluorine levels for formulation purposes, not as a variation for quality control purposes. To avoid possible misinterpretation of the concentrations for fluoride dentifrices, the agency is proposing the following ranges of concentrations for fluoride ingredients in the monograph that correspond to a range of 850 and 1,150 ppm theoretical total fluorine: For sodium fluoride a range of 0.188 to 0.254 percent, for sodium monofluorophosphate a range of 0.654 to 0.884 percent, and for stannous fluoride a range of 0.351 to 0.474 percent.

The agency agrees with the comments that the Panel's recommended limits for specific gravity are inadequate to accommodate new dentifrices utilizing less dense abrasive systems. In addition, the agency believes that changing the Panel's recommended limits for specific gravity from 1.3 to 1.7 to 1.1 to 1.7 to accommodate less dense abrasive systems will not have a significant impact on the effectiveness of a fluoride dentifrice and finds a specific gravity range of 1.1 to 1.7 appropriate for fluoride dentifrices.

However, the agency acknowledges that changes in specific gravity result in a corresponding change in the amount of fluoride contained in a given volume of a dentifrice if the concentration of the fluoride is expressed as a weight to weight measurement such as ppm. As the specific gravity value decreases, the amount of fluoride in a given volume of dentifrice also decreases. Because the agency agrees with one comment that, in general, the consumer is more likely to dispense a dentifrice on a toothbrush on the basis of volume or size of a ribbon, rather than to dispense a dentifrice on the basis of weight, the agency is concerned that at some lower limit of the amount of fluoride in a given volume of dentifrice, the amount of fluoride delivered on the toothbrush may be insufficient to provide an effective anticaries benefit. In addition, at some upper limit of the amount of fluoride in a given volume of dentifrice, the amount of fluoride delivered on the toothbrush will unnecessarily exceed the amount of fluoride needed to provide an effective anticaries benefit. In recommending that limits be required for both the specific gravity and the theoretical total fluorine ppm (a weight to weight measurement), the Panel, in effect, placed limits on the amount of fluorine per unit volume of toothpaste. For example, the Panel's lower limits of 900 ppm and a specific gravity of 1.3 convert to 1.17 mg fluorine per milliliter (mL) toothpaste; while the Panel's upper limits of 1,100 ppm and a specific gravity of 1.7 convert to 1.87 mg fluorine per mL toothpaste. Thus, the Panel's recommendations limit the amount of theoretical total fluorine in a dentifrice to a range of 1.17 to 1.87 mg per mL.

The agency is considering whether, in addition to providing ranges for fluoride dentifrices in terms of specific gravity and theoretical total fluorine measurements, it may be appropriate to provide ranges for fluoride dentifrices in terms of weight to volume measurements that correspond directly to the allowable ranges for specific gravity (1.1 to 1.7) and theoretical total fluorine (850 to 1,150 ppm) for dentifrice formulations utilizing abrasive systems that result in products having a specific gravity lower than 1.1 or higher than 1.7. Such abrasive systems would require modification of the specific gravity range because the specific gravity of the dentifrice is below 1.1 or above 1.7. The agency believes that the following guidelines for such dentifrices can be provided without unduly complicating the requirements for fluoride 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 fluorine per mL toothpaste and 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

fluorine per mL toothpaste, i.e., a range of 0.935 to 1.955 mg fluorine per mL. These limits would obviate the need to modify these ranges in the future.

The agency believes that a range of 0.935 mg to 1.955 theoretical total fluorine per mL of dentifrice may be an appropriate guideline for all Category I fluoride compounds, formulated in dentifrices with specific gravities less than 1.1 or greater than 1.7. This range ensures that dentifrices with lower or higher specific gravities due to changes in abrasives will remain in the same range of total fluorine per volume of dentifrice as currently marketed fluoride dentifrices that are within the range of 850 ppm to 1,150 ppm total fluorine and the range of 1.1 to 1.7 for specific gravity. In addition, the range above of total fluorine per volume of dentifrice for dentifrices with specific gravities above 1.7 or below 1.1 provides flexibility in the requirements for fluoride dentifrices to accommodate the development of new abrasive systems. The agency requests specific comment on the modification summarized above of the Panel's recommended ranges for theoretical total fluorine and specific gravity as set forth in the advance notice of proposed rulemaking (45 FR 20677) to provide a range of 0.935 to 1.955 mg theoretical total fluorine per mL of dentifrice for dentifrices with a specific gravity lower than 1.1 or higher than 1.7.

References

(1) Fogels, H. R., et al., "The Relative Caries-inhibiting Effects of a Stannous Fluoride Dentifrice in a Silca Gel Base," *Journal of the American Dental Association,* 99:456–459, 1979.

(2) Abrams, R.G., and D.W. Chambers, "Caries-inhibiting Effect of a Stannous Fluoride Silica Gel Dentifrice: A Three-year Clinical Study," *Journal of Clinical Preventive Dentistry,* 2:22–27, 1980.

(3) Triol, C.W., C.J. Wilson, and A.R. Volpe, "Effect on Caries of Two Monofluorophosphate Dentifrices in a Nonfluoridated Water Area: A Thirty-one Month Study," *Journal of Clinical Preventive Dentistry,* 3:5–7, 1981.

7. In an effort to clarify unresolved questions concerning the Panel's recommended LTP standards for fluoride dentifrices, the agency posed specific questions concerning the LTP's for discussion at a public meeting held on September 26 and 27, 1983. The agency questioned whether the Panel's recommended biological testing standards are necessary in addition to analytical testing to ensure the effectiveness of fluoride dentifrices (48 FR 38853).

In response to the agency's questions, the American Dental Association (ADA) submitted a comment (Ref. 1) stating that, ideally, the question of whether fluoride in a dentifrice is taken up by the tooth enamel to produce an effect on tooth structure that will make the tooth resistant to dental caries is best answered through well-controlled clinical tests. ADA added that other in vitro or in situ tests or animal studies, such as the biological tests recommended by the Panel, are also helpful in determining the anticaries effectiveness of fluoride dentifrices. ADA noted that enamel solubility reduction tests are most meaningful for fluoride dentifrices containing stannous fluoride. ADA also suggested that another method, now available, to evaluate the effect of fluoride on tooth structure is an evaluation of the ability of the product to induce remineralization of tooth structure. Another comment stated that the Panel's recommended tests should be continued for anticaries products, but other tests such as remineralization tests can be added to the Panel's recommended tests to demonstrate the clinical effectiveness of fluoride dentifrices. The comment explained that the remineralization test is particularly valuable in demonstrating clinical effectiveness.

A comment from a manufacturers' association agreed with the Panel's recommendation that all Category I fluoride dentifrices must meet the test requirements of any two of the following biological tests: (1) An enamel solubility reduction test, (2) a test for fluoride uptake by enamel; or (3) an animal caries reduction test. However, another manufacturers' association, representing many of the same dentifrice manufacturers, subsequently stated that the biological tests listed above would not be necessary for fluoride dentifrice formulations that are the same as the fluoride ingredients and abrasives listed in the LTP tables because the clinically proven effectiveness of these formulations that were reviewed by the Panel discounts any adverse effects of the abrasive on the biological activity. Therefore, the assurance of sufficient available fluoride ion and appropriate pH and specific gravity of the new formulation are all that is required. The comment recommended that biological testing be required only for new fluoride dentifrice formulations that were not reviewed by the Panel. In addition, the same manufacturers' association later commented that industry believes that other tests, e.g., remineralization tests, while interesting, are still of more academic than practical value. Industry does not consider any particular remineralization test as having been validated, and, therefore, it considers the addition of requirements for testing for remineralization properties to be unacceptable for regulatory purposes.

The Panel believed, and the agency concurs, that the demonstration of the bioavailability of the fluoride ion in two of the three biological tests, i.e., enamel solubility reduction, fluoride uptake by enamel, and/or animal caries reduction, is necessary to ensure the anticaries effectiveness of fluoride dentifrices, and the agency has included this requirement in the proposed monograph. Although the agency commends and encourages the development of additional testing procedures, such as remineralization tests, the agency believes that the three biological tests recommended by the Panel are adequate and sufficient to demonstrate the bioavailability of the fluoride ion in dentifrices. In addition, the Panel's recommendations concerning these three biological tests were based on the results of actual biological tests performed on fluoride dentifrices that had been shown to be clinically effective in preventing caries. The agency does not believe that there are sufficient data to correlate specifically the results of remineralization tests with clinical studies that demonstrate the anticaries effectiveness of fluoride dentifrices. Therefore, at this time, the agency believes that remineralization tests cannot be considered an adequate substitute for the Panel's recommended biological tests or that remineralization tests should be required in addition to the Panel's recommended tests. However, the agency recognizes that testing technology continues to evolve and has provided in the monograph the opportunity for interested persons to propose modifications or alternative testing procedures through the petition process established in 21 CFR 10.30.

With respect to a manufacturers' association's suggestion that biological testing is not necessary for fluoride dentifrice formulations that are the same as those that were reviewed by the Panel and listed in the LTP tables and its suggestion that only the analytical portion of the Panel's recommended testing be required for such dentifrices, the agency at this time does not have adequate information to show that biological testing is not necessary for such dentifrices. The Panel's recommendations were based on the correlation of laboratory testing results with clinical data. 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. Therefore, it is the responsibility of manufacturers to ensure that their fluoride dentifrice formulations demonstrate the bioavailability of the fluoride in two of the three biological tests, i.e., enamel solubility reduction, fluoride uptake by enamel, and/or animal caries reduction, as determined by the testing methods on file in the Dockets Management Branch under Docket No. 80N–0042, labeled as *Biological Testing Procedures for Fluoride Dentifrices.*

Reference

(1) Comment No. C00038, Docket No. 80N–0042, Dockets Management Branch.

8. Another question raised by the agency at the public meeting held on September 26 and 27 concerned how reference formulations that are required to interpret the results of biological testing would be available to manufacturers interested in marketing fluoride dentifrices if biological testing is necessary.

In response to the agency's concerns, ADA recommended that consideration be given to establishing United States Pharmacopoeia (USP) reference standards for fluoride dentifrice formulations that have been demonstrated to be clinically effective. ADA stated that manufacturers of these dentifrices should be responsible for establishing the formulas for these products with USP. In addition, the formulas should include complete instructions for their preparation so that USP can maintain appropriately prepared reference standards that are properly aged, freshly prepared, or in a stable formulation as determined by the manufacturer or manufacturers of the clinically tested product. ADA also suggested that the manufacturers, perhaps through a manufacturers' association, could recommend appropriate statistical procedures to be used for evaluating products in the biological tests that utilize the reference formulations.

A comment from a manufacturers' association objected to establishing USP reference standards for use in analytical testing and biological testing of fluoride dentifrices. The association stated that any marketed fluoride dentifrice can be used as a reference standard if it contains a particular fluoride ingredient and abrasive included in the LTP tables that have been demonstrated to be effective by appropriate clinical trials. The association contended that it is the responsibility of the "experimentor" to ensure that the fluoride dentifrice drug product chosen to serve as a reference formulation meets the fresh and aged minimal fluoride values and pH values and that it is within the allowable specific gravity range specified by the LTP's for that particular reference formulation. In addition, the particular fluoride ingredient contained in the chosen reference formulation must be the same as the fluoride ingredient in the dentifrice formulation being tested. The association recommended that, if a manufacturer cannot readily purchase or obtain a particular reference standard, it should be allowed to prepare a reference formulation based on formulas either published in the scientific literature with the results of clinical trials included or submitted to the agency by a manufacturers' association (Ref. 1). Again, the "experimentor" should be responsible for ensuring that the reference dentifrice that is formulated meets the appropriate testing standards set forth by the Panel in the LTP tables. Also, the reference formulation and the new fluoride dentifrice formulation being tested must score significantly higher than a placebo in the biological tests as "a simple check on the effectiveness."

In response to the agency's concerns regarding the stability of reference formulations, the manufacturers' association stated that requirements for minimal aged fluoride concentration in the LTP tables abrogates any concern regarding the stability of a reference formulation. The comment stated that "a candidate formulation that requires only analytical or analytical and biological laboratory testing is to be compared with the reference both fresh and aged, so that questions of stability are automatically answered."

In a later comment to the agency (Ref. 2), the manufacturers' association submitted offers, from four manufacturers, to voluntarily supply reference formulations to requestors having a legitimate interest in the manufacture of fluoride dentifrices. The reference formulations that would be supplied by these manufacturers would be certified that they conform to the monograph definition of effectiveness. These reference formulations would be for use only as a reference formulation in order to conduct required laboratory tests. As proposed by the comment, the manufacturers that volunteered to provide reference formulations could also elect to supply formulation information including exact ingredient percentages for a reference formulation. All of the manufacturers offered to provide fluoride dentifrice reference formulations for products currently manufactured by their company and to supply analytical certification of the reference formulation consisting of actual test values for total fluoride content, available fluoride ion content, pH, and specific gravity, as well as information concerning the date and place of manufacture, date of analysis, and storage recommendations for the reference dentifrice. The comment stated that the only analytical measurements that the manufacturers have agreed to provide for the certified reference formulations are available fluoride ion content, pH, and specific gravity, and that the purpose of the reference formulations is to provide a comparison of the laboratory values obtained in the biological tests. Therefore, it is not appropriate or necessary to require that these reference formulations be used to provide a comparison of the laboratory values obtained in the analytical tests. The manufacturers agreed to supply only an amount of the reference formulation that would be required for laboratory testing and some manufacturers limited the number of times per year that they would be willing to supply reference formulations to a particular requestor. The manufacturers stated that it would be the responsibility of the requestor (1) to allow 90 days for delivery of the reference formulation, (2) to use the reference formulation within a period of 90 days of certification to maintain validity of the certified values, (3) to determine which biological tests are to be performed, and (4) to store the reference formulation in the manner stated in the analytical certification. The costs of the reference formulation, including certification costs, would be borne by the requestor.

The agency agrees with ADA that fluoride dentifrice reference standard formulations that are required to interpret the results of the biological testing proposed in the monograph should be established as USP reference standards for fluoride dentifrice formulations. The validity and reliability of the results of biological testing to establish the effectiveness of fluoride dentifrice formulations are dependent on the quality, uniformity, validity, and reliability of the reference standard formulation used for comparison with the fluoride dentifrice formulation being tested. The agency is currently coordinating with USP to establish fluoride dentifrice reference standard formulations that will be made available to manufacturers interested in manufacturing fluoride dentifrices. Information concerning these reference standards will be on file in the Dockets Management Branch under Docket No.

80N–0042, labeled *Biological Testing Procedures for Fluoride Dentifrices.*

The agency appreciates the offers of several manufacturers to voluntarily provide certified reference formulations for use in the biological testing of fluoride dentifrices to other manufacturers that wish to manufacture fluoride dentifrices, but believes that this is not an appropriate mechanism to make such reference formulations available. The agency also believes that, although many manufacturers who are interested in marketing fluoride dentifrices could formulate adequate reference standard formulations based on information submitted to the Panel (Ref. 1), other manufacturers may not be able to do so. Because the use of an adequate reference standard is pivotal in producing valid results in the biological tests, the agency is proposing that manufacturers be required to establish the effectiveness of their fluoride dentifrice formulations in two of the three biological tests specified in the monograph using a USP fluoride dentifrice reference standard formulation, which should be available before this final monograph becomes effective. The agency clarifies that this requirement is not intended to apply to the use by manufacturers of in-house fluoride dentifrice reference standards for quality control purposes.

References

(1) OTC Volume 080253.

(2) Comment No. C00044, Docket No. 80N–0042, Dockets Management Branch.

9. One comment stated that the availability of reference standard formulations in quantities sufficient to adequately conduct research in developing new anticaries agents is imperative. Although manufacturers have stated that supplying reference formulations in such quantities would be a hardship on manufacturers of the reference formulations, the comment stated that, without such reference formulations, the results of any clinical trial would be ambiguous at best.

The scope of this rulemaking does not address requirements relating to dental research to develop new anticaries agents. Therefore, the agency will not discuss the availability of reference standard formulations for such use in this rulemaking.

10. Two comments requested that the Panel's recommended requirement for the numerical score in the biological tests for all Category I fluoride dentifrices be changed from "no lower than the score for a reference formulation at the 90-percent confidence level" to "not significantly lower than the score for the reference formulation." (See 45 FR 20677 to 20678.) One comment claimed that the 90-percent confidence limit can be misleading and can actually reward a poorly conducted set of laboratory tests. The comments suggested that appropriate statistical methods be used and that the choice of the statistical method be left up to the experimenter.

The agency agrees with the comments. The more general statement "not significantly lower than the score for the reference formulation" allows the application of appropriate statistical criteria to laboratory data to demonstrate that fluoride dentifrices achieve scores in the biological tests that are not significantly lower than the scores for the reference formulations.

The Panel recommended that the numerical score in the biological tests for fluoride dentifrices be "no lower than the score for a reference formulation at the 90-percent confidence level" to demonstrate bioavailability of the fluoride ion in that the dentifrice will alter tooth structure to make the tooth resistant to caries. Although the 90-percent confidence level as a statistical criterion may be acceptable for evaluating some biological test data sets, it is not necessarily acceptable for evaluating all biological test data sets. Therefore, the agency accepts the comment's suggested general statement. Further, as stated in § 211.165(d), appropriate statistical quality control criteria must be used for drug products.

C. Comments on Abrasive Systems for Anticaries Drug Products

11. One comment from a manufacturer disagreed with the Panel's recommendations concerning testing guidelines for Category I fluoride ingredient/abrasive combinations not specifically reviewed by the Panel. The comment contended that the Panel's recommendation to require such a new formulation to have laboratory testing values equal to or greater than the highest fluoride values listed in the Panel's LTP tables for the particular fluoride compound used in the formulation (45 FR 20677) is faulty. The comment stated that this recommended requirement must be changed to further reduce the probability that a clinically ineffective product will be marketed and accepted by consumers as effective. The comment argued that the highest values for fluoride ion in the Panel's LTP tables were based on specific formulations that had been clinically proven effective and that could be compared with appropriate reference formulations. The comment stated that these fluoride ion values would be acceptable for formulations similar to those included in the LTP tables, but would be too low to ensure the effectiveness of Category I fluoride ingredients formulated with an abrasive different from the specific formulations reviewed by the Panel. The comment recommended that such formulations be required either to establish effectiveness in a well-controlled clinical study or to maintain a minimum available fluoride ion level of 80 percent of the theoretical fluoride ion content, i.e., 800 ppm or above, throughout the formulation's proposed life.

In support of its position, the comment pointed out that in a 3-year clinical study submitted to the Panel for a fluoride dentifrice containing sodium fluoride and a magnesium silicate abrasive, the formulation was not significantly different from placebo in reducing caries (Ref. 1). Two other sodium fluoride dentifrice formulations (with high-beta-phase calcium pyrophosphate as the abrasive) were found to be effective in the same clinical study. The comment urged the agency to adopt the more conservative position of requiring either clinical studies or a minimum available fluoride ion level of 80 percent of the theoretical fluoride ion content for a Category I fluoride ingredient/abrasive combination not specifically reviewed by the Panel.

A comment from another manufacturer supported the use of nonclinical LTP's to establish the effectiveness of fluoride dentifrice formulations not specifically reviewed by the Panel and urged the agency to avoid the imposition of unnecessary, burdensome, and costly clinical testing of these drug products. The comment argued that the availability of the fluoride ion in fluoride dentifrice formulations is the essential factor for establishing the effectiveness of such dentifrices. The comment stated that, for the three fluoride ingredients recommended as Category I by the Panel, the ability of a dentifrice to provide available fluoride need not be determined by lengthy, burdensome clinical trials, but can be readily established by laboratory testing procedures designed to determine that the profile of the test dentifrice is comparable to the profile of a reference dentifrice. The comment contended that laboratory testing results for fluoride dentifrices are predictive of effectiveness and, in many instances, are a better indicator of anticaries effectiveness than clinical trials. The comment argued that laboratory tests can be done quickly and under rigid controls, whereas clinical trials take years and create tremendous logistic

difficulties. The comment stated that, because of the difficulties with clinical trials, clinical studies occasionally produce negative results, even where the effectiveness of the fluoride dentifrice is unquestioned. For this reason, the comment questioned the negative results of the clinical study discussed by the first comment above that did not demonstrate an anticaries effect for a sodium fluoride formulation containing a magnesium silicate abrasive. The comment stated that, as a matter of statistical probability, negative clinical results occur with effective dentifrices and cited an example of one such negative study on a dentifrice formulation that is widely accepted as an effective fluoride dentifrice. The comment added, moreover, that the information submitted to the Panel concerning the clinical trial and the laboratory testing data for the questionable sodium fluoride dentifrice containing magnesium silicate is insufficient to adequately evaluate the results of the clinical trial or laboratory testing.

In addition, the comment contended that the requirement of clinical testing for Category I fluoride ingredient/abrasive combinations not specifically reviewed by the Panel, when laboratory testing is adequate to demonstrate effectiveness, would be contrary to established principles of public policy. The comment explained that requiring high cost clinical studies would divert resources away from more worthwhile research; would be a financial burden, especially for smaller manufacturers, and decrease their ability to compete in the marketplace; and would also violate the purpose of the OTC drug monographs to set forth recognized standards of safety and effectiveness that new products can meet without going through full-scale clinical trials. The comment requested the agency to reject a requirement that clinical trials for effectiveness be conducted for Category I fluoride ingredient/abrasive combinations in dentifrice formulations not specifically reviewed by the Panel. The comment concluded that such a requirement would be unnecessary, burdensome, and cause costly duplicative clinical testing for such formulations.

Comments from a manufacturers' association stated that a new combination of an accepted fluoride source with an abrasive in a dentifrice formulation not specifically reviewed by the Panel should be evaluated as effective if it meets the appropriate parameters for availability of the fluoride ion in the Panel's recommended analytical and biological tests as well as appropriate parameters for theoretical total fluorine content and specific gravity.

The comment specified the following requirements as appropriate for determining the effectiveness of fluoride dentifrice formulations not specifically reviewed by the Panel:

(1) Theoretical total fluorine concentration between 850 and 1,150 ppm, and

(2) Specific gravity within the range 1.1 to 1.7, and

(3) Meet the most stringent of analytical profiles for a fresh and aged product for the particular fluoride ion source, and

(4) Demonstrate that scores on 2 of 3 of the biological tests specified in the monograph are not significantly lower than a reference formulation using the same fluoride source, and are significantly higher than a placebo;

or

(1) and (2) above, and

(5) Demonstrate through appropriate clinical trials that the formulation is effective.

The comment added that "attempting to ensure exact equivalency between various possible reference formulations is not only unwarranted, but could be construed as providing an unfair advantage to existing marketed products, without an adequate scientific basis."

Another comment agreed with the requirements for new fluoride dentifrices that were recommended by the manufacturers' association above. In addition, the comment requested that the agency provide a procedure to add new "reference fluoride/abrasive combinations" to the LTP tables when such fluoride dentifrice formulations are proven effective in a clinical study. The comment suggested a procedure whereby the agency could be petitioned to include a new formulation in the LTP's and supporting documents would be placed in the public docket. A **Federal Register** notice could be published to advise the public of the petition, to invite comment, and to provide an opportunity for an oral presentation. Based on the information received, the agency could then publish a final decision concerning whether or not to add the new fluoride dentifrice formulation to the LTP's. The comment believed that such a procedure would be particularly appropriate if the LTp's are set out in "guidelines" as opposed to regulations and pointed out that such a procedure is commonly used by other Federal agencies in setting new reference standards.

A comment from ADA suggested that standards for Category I fluoride ingredient/abrasive combinations in dentifrice formulations not specifically reviewed by the Panel include remineralization testing. ADA added that it will continue to require clinical studies to validate the effectiveness of such new formulations for its "Acceptance Program."

The agency concurs with the panel's recommendations that a Category I fluoride ingredient/abrasive combination in a dentifrice formulation, not specifically reviewed by the Panel, be required to contain an amount of available fluoride ion equal to or greater than the highest available fluoride ion value recommended for the specific fluoride ingredient, i.e., an amount of available fluoride ion equal to or greater than the highest value listed in the active ingredient list in the monograph for the specific fluoride ingredient. This requirement applies to fluoride dentifrices that contain a Category I fluoride ingredient and either a new abrasive ingredient not previously included in marketed dentifrices or an abrasive ingredient included in previously marketed dentifrices in a fluoride ingredient/abrasive combination not specifically reviewed by the panel.

The agency believes that it is unnecessary to require that Category I fluoride ingredient/abrasive combinations in dentifrice formulations not specifically reviewed by the Panel contain 80 percent of the theoretical amount of total fluorine in the formulation as available fluoride ion throughout the period of intended use, as one comment requested. The comment's contention that data it submitted to the panel show that a sodium fluoride Dentifrice containing a magnesium silicate abrasive is ineffective in a clinical study even though laboratory tests show that the dentifrice would meet the Panel's LTP standards (Ref. 1) was baaed on (1) a table and a short discussion presenting a summary of laboratory test results for the sodium fluoride dentifrice containing magnesium silicate and two other sodium fluoride dentifrices; and (2) a table presenting a summary of the clinical trial results for the same sodium fluoride dentifrice containing magnesium silicate and the two other sodium fluoride dentifrices. Information concerning the details of the laboratory testing methods, the raw data, the analysis of the data for the laboratory tests, the details of the clinical trial for the sodium fluoride dentifrice containing magnesium silicate, and the details of

the statistical analysis of the clinical data for this dentifrice were not submitted. The panel reviewed the information above concerning the sodium fluoride dentifrice containing magnesium silicate and concluded that this information is inadequate to justify changing the Panel's recommendation that Category I fluoride ingredient/abrasive combinations in dentifrice formulations not specifically reviewed by the Panel be required to contain an amount of available fluoride ion equal to or greater than the highest available fluoride ion value required for the specific fluoride ingredient (Ref. 2). The agency concurs with the Panel and agrees with another comment that the submitted information is inadequate to conclude that the dentifrice was in fact ineffective or that the dentifrice tested in the clinical study did in fact meet the panel's LTP standards.

The panel based its development of LTp's on laboratory testing results from studies on fluoride dentifrice formulations that had actually been clinically treated and found effective. The agency is unaware of any data, other than the data concerning the sodium fluoride dentifrice containing a magnesium silicate abrasive discussed above, that would indicate that a dentifrice which meets the Panel's recommended standards for Category I fluoride ingredient/abrasive combinations in dentifrice formulations not specifically reviewed by the Panel has been found to be ineffective in preventing caries. To the contrary, the Panel stated that the extensive amount of testing of the Category I fluoride ingredients, which includes laboratory, animal, and clinical tests, allows predictions as to which dentifrice formulations will be effective. The Panel therefore concluded that if certain analytical and biological tests are conducted and acceptable test values are achieved, clinical testing is not required (45 FR 20677).

The agency believes that the Panel's recommended standards are applicable to all new Category I fluoride ingredient/abrasive combinations in formulations that contain a fluoride ingredient specified in the monograph. Therefore, it is unnecessary to specifically add Category I fluoride ingredient/abrasive combinations in dentifrice formulations not specifically reviewed by the Panel to the LTP tables through a petition procedure as suggested by one comment.

Based on the Panel's recommendations, the agency is proposing that the requirements for available fluoride ion for each fluoride ingredient listed in the monograph without a specified abrasive also apply to Category I fluoride ingredient/abrasive combinations in dentifrice formulations not specifically reviewed by the Panel. The agency has not included specific abrasives in the active ingredient list with the exception of the special case of a stannous fluoride dentifrice containing calcium pyrophosphate as an abrasive. (See comment 4 above.) In addition, Category I fluoride ingredient/abrasive combinations in dentifrice formulations not specifically reviewed by the Panel must meet the biological testing requirements proposed in the monograph and conform to FDA's current good manufacturing practice regulations (21 CFR Part 211) with respect to other parameters discussed by the Panel such as specific gravity and pH. Such Category I fluoride ingredient/abrasive combinations in dentifrice formulations must also conform to regulations concerning whether inactive ingredients are safe and do not interfere with the effectiveness of the product in preventing caries (21 CFR 330.1(e)). (See comment 4 above.)

While the agency encourages the development of new testing technology for fluoride dentifrices, such as remineralization testing, the agency does not believe it is necessary to add a requirement for such testing for new fluoride dentifrice formulations in addition to the Panel's recommended testing requirements. As stated above, the agency has accepted the Panel's recommended requirements as adequate to demonstrate the anticaries effectiveness of Category I fluoride ingredient/abrasive formulations not specifically reviewed by the Panel.

References

(1) Comment No. C00016, Docket No. 80N-0042, Dockets Management Branch.

(2) OTC Volume 08APA2, Summary Minutes of the 43rd Meeting of the Panel, April 26, 27, and 28, 1978, Docket No. 80N-0042, Dockets Management Branch.

12. Four comments requested that additional abrasive ingredients be included in the laboratory testing profile table for sodium fluoride dentifrices. Three comments expressed concern that silica was not specified in "Table 1—Acceptable Test Values for Sodium Fluoride Dentifrices" (45 FR 20679) as an allowable abrasive for sodium fluoride dentifrices. One of the three comments noted that silica is listed as an abrasive for sodium monofluorophosphate and stannous fluoride dentifrices. The comment stated that because the Panel found silica to be a safe and effective abrasive, as evidenced by its inclusion with the other Category I fluoride dentifrices, there is no reason why it should not be included in sodium fluoride preparations.

The second comment submitted the results of two well-controlled 3-year clinical studies to demonstrate the anticaries effectiveness of a 0.243-percent sodium fluoride/silica dentifrice, and also proposed a testing profile for this formulation, with a pH of 6.0 to 8.5, for inclusion in the laboratory testing profile tables (Ref. 1). The third comment referred to the second comment's submission (Ref. 1), agreed that the proposed testing profile should be adopted (Ref. 2), and added that its own sodium fluoride/silica dentifrice formulation (pH 4.5 to 5.5) was bioequivalent to the dentifrice (pH 7.2) submitted by the second comment with respect to fresh total fluoride, fresh soluable fluoride, and aged soluble fluoride. According to the comment, both formulations, when compared with a placebo dentifrice control, significantly reduced caries ($p < 0.05$) in rats, thus meeting the accepted animal caries reduction protocol as specified by the Panel (Ref. 2). Based on the submitted data, the comment requested that the pH range in the test profiles for sodium fluoride/silica dentifrices be expanded to 4.5 to 8.5.

The fourth comment requested that sodium bicarbonate be included in the laboratory testing profile tables as an acceptable abrasive for sodium fluoride dentifrices. The comment submitted data from a 2-year clinical study that showed the sodium fluoride/sodium bicarbonate combination to be effective in reducing calories in school children (Ref. 3) and included a review of this study (Ref. 4). The comment also referred to another submission to the Panel that contained data showing a sodium fluoride/sodium bicarbonate dentifrice to be effective with available fluoride levels between 500 to 1,100 ppm (Ref. 5). The comment recommended raising the minimum available fluoride standards in "Table 1—Acceptable Test Values for Sodium Fluoride Dentifrices" (45 FR 20679) to a level of 850 ppm for both the fresh and the aged dentifrices, and recommended a pH range of 7.5 to 8.5.

As discussed in comment 4 above, the test values listed in the tables represent actual test values obtained from analyzing dentifrices that were used in clinical trials and found to be effective anticaries drug products. The Panel recommended that a fluoride dentifrice product containing a Category I fluoride ingredient/abrasive formulation could be marketed if the product meets or

exceeds the available fluoride ion levels listed in the LTP tables and meets other parameters set by the Panel, such as limits for specific gravity and pH, and biological testing standards (45 FR 20677 to 20681).

After extensive review, the agency has determined that the availability of the fluoride ion in the formulation and meeting the biological testing requirements are the most important testing criteria for predicting the effectiveness of a fluoride dentifrice product and has specified these requirements in the proposed monograph. The agency considers the existing regulations in 21 CFR Parts 211 and 330 adequate to address the product's professed standards of identity, strength, quality, and purity with respect to parameters such as specific gravity and pH. (See comment 4 above.) Therefore, it is not necessary to include such parameters for additional Category I fluoride/abrasive combinations in the monograph; nor is it necessary to change the Panel's recommendations regarding specific pH guidelines for particular fluoride dentifrice formulations. (See comment 5 above.) Because biological testing and the availability of fluoride ion are the key factors in determining the effectiveness of the dentifrice formulation, the agency is proposing to include new § 355.70 concerning biological testing requirements and to include in the active ingredient section of the tentative final monograph (§ 355.10(a)) the required amount of available fluoride ion for each Category I fluoride active ingredient in a dentifrice dosage form. Manufacturers must ensure that their products meet the biological testing requirements and contain the amount of available fluoride ion specified in the final monograph. (See comment 4 above.)

Accordingly, the agency is proposing that any Category I fluoride compound formulated with an appropriate abrasive can be marketed provided the dentifrice meets the biological testing requirements stated in § 355.70 and contains the amount of available fluoride ion stated in § 355.10(a). (See comment 11 above.) Thus, for a sodium fluoride and silica formulation or a sodium fluoride and sodium bicarbonate dentifrice, the formulation must meet the biological testing requirements and the available fluoride ion concentration must be equal to or greater than 650 ppm. (See § 355.70 and § 355.10(a) of this tentative final monograph.)

References

(1) Comment No. C00037, Docket No. 80N–0042, Dockets Management Branch.

(2) Comment No. C00044, Docket No. 80N–0042, Dockets Management Branch.

(3) Torell, P., and Y. Ericsson, "Two-Year Clinical Tests with Different Methods of Local Caries-Preventive Fluorine Application in Swedish School Children," *Acta Odontologica Scandinavica*, 23:287–322, 1965.

(4) Comment No. CR0006, Docket No. 80N–0042, Dockets Management Branch.

(5) OTC Volume 080134A.

13. One comment expressed concern that powdered fluoride dentifrices and "sodium bicarbonate-based sodium fluoride dentifrices" would not be covered as anticaries drug products under the recommended monograph. The comment raised this concern because it felt that the Panel's recommended specific gravity limits, while acceptable for normal paste dentifrices, are not reasonable for powdered dentifrices, which have lower densities then those recommended in the Panel's specific gravity standard. The comment suggested that a separate standard for these lower density powders be developed that would provide effective levels of fluoride ion and submitted a chart comparing fluoride dosage limits for powders and pastes (Ref. 1). The comment also suggested that the appropriate parameter for powdered fluoride dentifrices would be a poured-bulk density range between 0.5 and 1.7 grams/milliliter (g/mL) because poured-bulk density is a more well-defined measure of the weight to volume relationship of powders than specific gravity.

The comment recommended two poured-bulk density standards for powdered fluoride dentifrices, i.e., 1.0 to 1.7 and 0.50 to 0.99 g/mL. The comment claimed that if the poured-bulk density is equal to or greater than 1.0 g/mL, the product can deliver an effective level of fluoride per application to the teeth. The comment stated that powdered dentifrices with a lower poured-bulk density (0.5 to 0.99 g/mL), such as sodium fluoride with sodium bicarbonate as an abrasive, could be aproved if it were demonstrated that the product delivers the same effective level of fluoride ion with two applications per brushing as would normally be applied in one application of a product with a bulk density of 1.0 to 1.7 g/mL. The comment suggested that the proper dosage of fluoride ion can be assured for powdered dentifrices by either requiring suitable minimum soluble fluoride specifications for powders and/or by requiring labeling instructions to the consumer to apply the product more than once per brusing. Another suggestion was to drop the Panel's specific gravity recommendations and instead require defined levels of fluoride ion in a set volume of the product, whether powder or paste. In addition, the comment stated that although the users of powdered dentifrices currently do not make up a large percentage of the population, this form of dentifrice may in the future prove ideal for certain beneficial properties, such as the reduced likelihood that the dry ingredients will interact adversely and inactivate the fluoride during storage of the dentifrice.

The agency has reviewed the comments and other information and determined that the information is insufficient to generally recognize powdered fluoride dentifrices as safe and effective. The agency is unaware of data in the literature that address the safety and effectiveness of powdered fluoride dentifrices, and invites submissions of such data if any are available.

The agency agrees that a poured-bulk density range is a more appropriate parameter for powdered fluoride dentifrices than a specific gravity range. However, the agency is unable to conclude that two ranges for poured-bulk density (0.5 to 0.99 g/mL and 1.0 to 1.7 g/mL) are necessary for powdered dentifrices nor is the agency convinced that two applications per brushing with a powdered dentifrice in the lower poured-bulk density range (0.5 to 0.99 g/mL) would provide an appropriate dose of fluoride. The agency is concerned that two applications of a powdered fluoride dentifrice to a toothbrush might provide an unnecessarily high level of the fluoride ion. For example, according to the table submitted by the comment (Ref. 1), powdered fluoride dentifrices with a poured-bulk density of 0.99 g/mL would provide 2,300 micrograms of available fluoride per dose assuming that 2 mL of the product is used per brushing (two 1 mL applications per brushing), whereas currently marketed pastes would provide not more than 1,870 micrograms of available fluoride per dose assuming that 1 mL of the product is used per brushing based on the Panel's recommended standards. The agency needs additional, more specific data (e.g., laboratory studies) demonstrating that a controlled volume of powdered fluoride dentifrice (e.g., 1 mL) consistently delivers a predictable and measurable safe and effective level of fluoride ion.

The comment did not provide directions for how a powdered fluoride dentifrice should be applied to a toothbrush, or provide data demonstrating how much fluoride ion

each brushing would deliver to the teeth. The agency has reviewed the labels for several previously marketed powdered fluoride dentifrices that contained directions for use. These directions varied according to the product's fluoride concentration. For example, the labeling of a 0.5-percent powdered sodium fluoride dentifrice directed the user to "pour ¼ teaspoonful (0.5 grams) in palm of hand. Wet toothbrush with water and brush teeth with this powder in usual manner twice daily, morning and night." The labeling also stated that children under age 6 should not use the product. The labeling directions for another powdered dentifrice containing 0.04 percent sodium fluoride stated "Use a small brush with bristle tufts spaced so that they fit the embrasures between the teeth. Place a thimble full of (product) in the palm of the hand and dip the wet brush into it. Place the bristles firmly on the teeth and with a gentle circular motion, scour the 'between the teeth' spaces. Swishing the brush backward and forward does not clean between the teeth where decay begins. Clean 3 to 4 teeth at a time and slowly brush around the whole mouth. The mouth should be well rinsed to remove all loosened debris. It is recommended that teeth be brushed AFTER breakfast and BEFORE retiring. The proper use of (product) refreshes the mouth and promotes oral hygiene. This dentifrice is not designed for children under 8 years of age." The labeling of a (currently marketed) powdered fluoride dentifrice that is manufactured in England did not contain any directions for use.

As there are several possible methods of applying the powdered dosage form to a toothbrush (e.g., placing the powder on the palm of the hand with a small amount of water and applying the slurry of the powder with a dry toothbrush, pouring the powder on a dampened brush, or dipping a wet brush into a dry powder, etc.), and because there does not appear to be any consistency in the amount of dentifrice that is recommended for use, the amount of fluoride ion delivered to the teeth may vary significantly. From the information available to the agency, there is no indication that previously or currently marketed powdered fluoride dentifrices provided a consistent amount of fluoride per brushing application. The agency cannot determine whether powdered fluoride dentifrices are safe and effective unless specific directions for use and data are provided demonstrating that the powdered fluoride dentifrice used per specific directions can deliver an amount of fluoride ion to the teeth equivalent to an amount delivered by a paste dentifrice. The directions for use need to be either relatable to the method used in a clinical study demonstrating efficacy or to laboratory studies demonstrating that the available fluoride ion is equal to or greater than the Panel's recommended 650 ppm for sodium fluoride.

The comment's submissions did not include directions for use of powdered fluoride dentifrices by children under 12 years of age. The agency is concerned that children under 12 years of age may have considerable difficulty in using a powdered fluoride dentifrice properly because the proper use of powdered dosage forms may require greater manual dexterity than the proper use of paste dosage forms and because of limited experience with this dosage form of a dentifrice. Unless data can be provided to show that children under 12 years of age can use powdered dentifrices properly, the agency believes, for safety and efficacy reasons, that a powdered fluoride dentifrice should not be labeled for use by children under age 6 and should be labeled for use by children ages 6 to 12 with adult supervision. A warning statement against use by children under 6 years of age is currently required by § 310.201(a)(10)(vi) (21 CFR 310.201(a)(10)(vi)) for sodium fluoride dentifrice powders, and the need for adult supervision for children ages 6 to 12 is considered consistent with the requirement for adequate directions for use in § 310.201(a)(10)(v) (21 CFR 310.201(a)(10)(v)). The agency is also concerned that the potential for a young child to accidentally consume a toxic amount of fluoride with a dentifrice in a powdered dosage form may be greater than with a paste dosage form. The agency is aware that paste fluoride dentifrices containing the package size limitations of 260 mg total fluoride have been marketed for many years and have not raised concerns of acute toxicity in young children. Although § 310.201(a)(10)(iv) (21 CFR 310.201(a)(10)(iv)) limits powdered sodium fluoride dentifrices to not more than 5 mg of sodium fluoride per g and not more than 300 mg of sodium fluoride per retail package, powdered fluoride dentifrices have had very limited marketing in this country and the agency is unaware of any data concerning the acute toxicity of powdered fluoride dentifrices in children.

The agency agrees that powdered fluoride dentifrices would probably remain 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. It also agrees that data submitted to the Panel (OTC Volume 080134A) support the stability of sodium fluoride/sodium bicarbonate toothpaste dentifrices. However, the storage conditions of a powdered fluoride dentifrice would have a significant impact on whether the powdered dentifrice would remain stable longer than the paste form. Storage of the product in the bathroom where the humidity is high due to showering and bathing would require that the container be moisture resistant to prevent moisture contamination of the powdered drug product. Although stability is an important factor, it is governed by the current good manufacturing practice regulations in §211.137(g) (21 CFR 211.137(g)) and is outside the scope of this rulemaking.

The agency is therefore proposing that powdered fluoride dentifrices as anticaries drug products be placed in Category III in this tentative final monograph for OTC anticaries drug products.

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

References

(1) Comment No. C00039, Chart labeled "*Table I:* Comparison of fluoride dosage limits provided under Church & Dwight powder recommendation with level achieved by paste following the OTC Advisory Panel specifications," Docket No. 80N-0042, Dockets Management Branch.

(2) Letter from W. E. Gilbertson, FDA, to W. R. Sorenson, Church & Dwight Co. Inc., coded LET009, Docket No. 80N-0042, Dockets Management Branch.

14. One comment expressed concern that the term "hydrated silica" is too broad to identify silica abrasives currently used in dentifrices. The comment stated that the Panel may have used this term because the term appeared in the *CTFA Cosmetic Ingredient Dictionary*. The comment noted that, "while this monograph incudes most of the currently used dentifrice silicas, it also includes sand. Further, there are no specific assay tests to identify the product." The comment recommended that the *Food Chemicals Codex* monograph for "silicon dioxide" in Edition III, be used to "define" silicas for dentifrices. The comment stated that this monograph includes most commonly used dentifrice silicas and excludes those silicas containing less than 94 percent silicon dioxide. The comment further explained that the monograph also includes only synthetic amorphous silicas, i.e., "fumed,

precipitated, hydrous silicas, and silica gels."

The agency notes that the terms used to identify ingredients in part I.B. of the Panel's report (45 FR 20669), where the term "hydrated silica" appears, were taken from the actual labels of products or from the lists of ingredients contained in the submissions to the Panel. These terms were listed exactly as they appeared in the product labels or the lists of ingredients in the submissions. The term "hydrated silica" also appears in parts I.C.2. as an inactive ingredient. The Panel did not consider this list all inclusive and took no position as to the value of these ingredients in dental products (45 FR 20669). The lists of ingredients in parts I.B. and I.C. of the Panel's report were not intended to identify specific ingredients that are appropriate for anticaries drug products.

Although the OTC drug review is an active, not an inactive, ingredient review, the Panel did discuss inactive ingredients such as silica that are included in dentifrices as abrasives because they are known to have an impact on the availability of the fluoride ion in fluoride dentifrices and, thus, have an impact on the effectiveness of these drug products (45 FR 20676 to 20677). The agency has found it necessary to include only one abrasive (calcium pyrophosphate for dentifrices containing stannous fluoride as the active ingredient) in the tentative final monograph. (See comment 4 above.) Because other fluoride dentifrices do not require a specific fluoride ion concentration for particular abrasives, it is not necessary for the agency to specify such abrasives in the monograph. In addition, the abrasives used in fluoride dentifrice drug products must meet the requirements for inactive ingredients in § 330.1(e) (21 CFR 330.1(e)) which states that "only suitable inactive ingredients which are safe in the amounts administered and do not interfere with the effectiveness of the preparation or with suitable tests or assays to determine if the product meets the professed standards of identity, strength, quality, and purity" may be used. Therefore, defining silicas for dentifrices is outside of the scope of this monograph.

15. One comment submitted an in vitro testing method for determining the abrasiveness of dentifrices on human dentin (Ref. 1).

The testing of the abrasivity of fluoride dentifrices is not being addressed in this tentative final monograph because abrasives are not considered to be active ingredients in these dentifrices. The OTC drug review is an active, not an inactive, ingredient review. Therefore, testing methods to determine the degree of abrasivity of fluoride dentifrices are not included in the tentative final monograph. However, as stated above, inactive ingredients such as abrasives are subject to the provisions in § 330.1(e) and must be safe for use in fluoride dentifrices.

Reference

(1) Comment No. C00042, Docket No. 80N–0042, Dockets Management Branch.

D. Comments on Labeling of Anticaries Drug Products.

16. One comment suggested that the labeling of fluoride dentifrices be based on volume rather than on weight. The comment stated that consumers dispense dentifrices by volume, not by weight, and that the "rest of the world" labels dentifrices by volume.

The agency disagrees with the comment's suggestion to label the amount of dentifrice contained in a package based on a volume measurement rather than a weight measurement. FDA regulations concerning declaration of net quantity of contents in 21 CFR 201.62(a) require that "The label of an over-the-counter drug in package form shall bear a declaration of the net quantity of contents * * * [and] the statement of quantity * * * shall be in terms of weight if the drug is solid, semisolid, or viscous * * *." Under this regulation, fluoride dentifrices in this country have been labeled with weight measurements to specify quantity for many years. Although consumers dispense dentifrices by volume rather than weight and other countries label dentifrices with volume measurements rather than weight measurements, consumers in this country are familiar with purchasing dentifrices based on weight rather than on volume. The comment did not submit any documentation to support this change in labeling from a weight to a volume basis. Accordingly, this suggestion is not being adopted.

17. Four comments expressed concern about the expiration dating for fluoride dentifrices. The comments agreed that the aged minimal fluoride ion values that appear in the Panel's LTP Tables 1, 2, and 3 (45 FR 20679 to 20681), for dentifrices found to be effective in clinical studies, should be used in determining an expiration date for the fluoride/abrasive dentifrices listed in the tables. One comment stated that expiration dating is the only appropriate way to provide the consumer with relevant information regarding the "freshness" of the product on the shelf, whereas "production dating," which provides in the labeling the date that a product was manufactured, is useless and might even mislead consumers because different product formulations will decline in fluoride concentration at different rates. Another comment stated that expiration dating is not needed for fluoride dentifrices that meet the requirements specified for the aged minimal fluoride ion concentration after 3 years, and that expiration dating would only be necessary for a dentifrice that falls below the minimal fluoride ion concentrations specified in the Panel's tables before it is 3 years old.

In response to the Panel's recommendation that expiration dating should conform to "good manufacturing practice," two comments expressed concern that this recommendation would be misunderstood. One comment stated that, although fluoride dentifrices are manufactured under current good manufacturing practice regulations in 21 CFR Part 211, the specific analytical soluble fluoride level that is the basis of an expiration date is different for each fluoride/abrasive combination and is well below an arbitrary level such as 80 or 90 percent of the total fluoride content which is often the intent when the term "good manufacturing practice" is used. The comments also noted that the Panel had recommended that an expiration date need be indicated only on the carton (outer package) of dentifrice drug products, and not on the immediate container. The comments suggested that a new section be added to the monograph as follows:

"§ 355.50(g) *Expiration dating.* Any expiration dating required by current good manufacturing practices for drugs may be marked only on the outer package of a dentifrice product so as to be visible at the time of purchase."

The agency agrees with one comment that it is unnecessary to require production dating of dentifrice products. Production dating is not as important to the consumer as an expiration date because the consumer is concerned only with the date after which the product may be ineffective. Production dating does not provide such information and, therefore, it is not being required for dentifrice drug products.

The agency agrees that the manufacturers should use the aged minimal fluoride ion limits provided in the LTP Tables as modified in comment 5 above to determine the expiration dates for fluoride dentifrices that will be covered by the final monograph. However, the agency is not including in the tentative final monograph the aged minimal fluoride ion values from the LTP tables. (See comment 4 above.) These aged minimal fluoride ion values

provide appropriate guidelines for determining the expiration date of a dentifrice and whether the expiration date should appear in the labeling of the product. The expiration date for such fluoride dentifrices should be the date when the soluble fluoride ion level of the aged dentifrice is equal to or lower than the fluoride ion level listed in the tables under "aged minimal fluoride ion value" for the particular fluoride/abrasive combination. FDA regulations concerning expiration dating in § 211.137(g) (21 CFR 211.137(g)) state that, pending consideration of a proposed exemption published in the **Federal Register** of September 29, 1978 (43 FR 45088), the expiration dating requirements of § 211.137 shall not be enforced for human OTC drug products if their labeling does not bear dosage limitations and the products are stable for at least 3 years as supported by appropriate stability data. At this time, in accordance with § 211.137(g), any fluoride/abrasive dentifrices that will maintain, for at least 3 years, levels of fluoride ion equal to or greater than the aged minimal fluoride ion values listed in the LTP tables as modified in comment 5 above will not be required to include an expiration date in the labeling.

For new fluoride/abrasive dentifrice formulations, the criteria for not requiring an expiration date will be dependent upon the product meeting the highest aged minimal value in the LTP tables as modified in comment 5 above for the particular fluoride compound. For example, the aged minimal fluoride ion values listed in Table III and modified in comment 5 above for the combination of stannous fluoride with different abrasives are 108 ppm and 650 ppm. The expiration date for a dentifrice containing stannous fluoride and a new abrasive would be the date after which the fluoride ion concentration falls below 650 ppm, the highest aged minimal fluoride ion value listed for stannous fluroide ion.

Regarding one of the comments' reference to the location of the expiration date in the labeling, § 201.17 (21 CFR 201.17) states that when an expiration date of a drug is required, it shall appear on the immediate container and also on the outer package. Therefore, if a fluoride dentifrice does not contain a fluoride ion level equal to or greater than the aged minimal level after 3 years, it will not meet the criteria of § 211.137(g), and the expiration date must appear on the immediate container and on the outer package under § 201.17. Because expiration dating for OTC drug products is addressed in the current good manufacturing practice regulations, it is unnecessary to include in this tentative final monograph the comment's suggested new § 355.50(g) regarding the requirement of expiration dating on the outside carton only.

18. One comment from a manufacturers' association stated that a Category I fluoride ingredient/abrasive combination not specifically reviewed by the Panel can be evaluated as effective if it gives acceptable results in the Panel's recommended analytical and biological testing. The comment asserted, however, that any extension of this concept, i.e., the use of results of such testing, to a comparative evalaution of effectiveness between different fluoride dentifrices is unwarranted because of the inherent variability of the biological tests with respect to specific fluoride ingredients.

The agency agrees with the comment that the extension of laboratory test data to a comparative evaluation of effectiveness between different fluoride dentifrices is inappropriate. Further, the agency believes that the use of comparative laboratory test data, resulting from the Panel's recommended testing standards for fluoride dentifrices or fluoride active ingredients, to infer that particular fluoride dentifrices or fluoride ingredients are more effective than other fluoride dentifrices or fluoride ingredients in preventing caries is not supportable. The agency is unaware of data that would support the conclusion that a fluoride dentifrice which is shown to be superior in laboratory tests when compared to other fluoride dentifrices is in fact clinically superior in its ability to prevent caries. The agency also believes that such comparative test data do not constitute an adequate basis for labeling claims of superior effectiveness and that such labeling would result in misbranding of the product.

II. The Agency's Tentative Conclusions on Anticaries Drug Products

A. Summary of the Agency's Changes in the Panel's Recommendations

1. The agency is proposing that the active ingredients identified in § 355.10(a) be revised to include the amount of available fluoride ion required for each Category I fluoride active ingredient in a dentifrice dosage form. The agency beliefves that it is necessary to require appropriate levels of available fluoride ion to ensure the anticaries effectiveness of these fluoride dentifrices. The agency has also added new § 355.70, Testing Procedures for Fluoride Dentifrice Drug Products, to include the Panel's recommended biological testing requirements for fluoride dentifrices because they are necessary to ensure the effectiveness of these products. (See comments 4 and 7 above.)

2. The agency is proposing ranges of concentrations for fluoride ingredients in dentifrice dosage forms in § 355.10(a) that correspond to a range of 850 to 1,150 ppm theoretical total fluorine. Providing ranges of concentrations for fluoride ingredients in dentifrices in the monograph clarifies that the allowable theoretical total fluorine range of 850 to 1,150 ppm is intended to allow a range of theoretical total fluorine levels for formulation purposes, not as a variation for quality control purposes. (See comment 6 above).

3. The agency is proposing the Panel's recommended laboratory testing requirements, as set forth in the Panel's LTP tables (45 FR 20679 to 20681) and revised in comments 5 and 6 above, as guidelines of appropriate testing limits for determining the specific gravity and pH of dentifrices containing monograph fluoride ingredients. Because these parameters are adequately addressed by the current good manufacturing practice regulations (21 CFR Part 211), the agency does not find it necessary to codify these LTP tables in the final monograph. (See comment 4 above.)

4. The agency has placed fluoride dentifrices containing theoretical total fluorine concentrations greater than 1,150 ppm, e.g., dentifrices containing 1,500 ppm theoretical total fluorine, in Category III. Data demonstrating an added anticaries benefit to perons who use a dentifrice containing 1,500 ppm theoretical total fluorine as compared to formulations contianing 1,150 ppm theoretical total are not publicly available at this time. (See comment 1 above.)

5. The agency has also placed fluoride dentifrices in a powdered dosage form in Category III. Sufficient data supporting the effectiveness of such dentifrices are necessary before they can be generally recognized as safe and effective. (See comment 13 above.)

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of Februry 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency

therefore concludes that no one of these rules, including the proposed rule for OTC anticaries drug products, is a major rule.

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

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

The agency has carefully considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch, Food and Drug Administration (address above) between 9 a.m. and 4 p.m., Monday through Friday. This action was considered under FDA's final rule implementing the National Environmental Policy Act (21 CFR Part 25).

Interested persons may, on or before October 13, 1988, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before October 13, 1988. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register**.

Interested persons, on or before June 15, 1989, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before August 15, 1989. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OCT drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA–305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on August 15, 1989. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register**, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

List of Subjects in 21 CFR Part 355

Labeling, Over-the-counter drugs, Anticaries drug products.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended in Part 355 (as established in the tentative final monograph published in the **Federal Register** of September 30, 1985; 50 FR 39854), as follows:

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

1. The authority citation for 21 CFR Part 355 is revised to read as follows:

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

2. Section 355.10 is amended by revising paragraph (a) to read as follows:

§ 355.10 Anticaries active ingredients.

* * * * *

(a) *Dentifrices.* (1) Sodium fluoride 0.188 to 0.254 percent with an available fluoride ion concentration ≥650 parts per million.

(2) Sodium monofluorophosphate 0.654 to 0.884 percent with an available fluoride ion concentration (consisting of $PO_3F^=$ and F^- combined) ≥800 parts per million.

(3) Stannous fluoride 0.351 to 0.474 percent with an available fluoride ion concentration ≥700 parts per million for products containing abrasives other than calcium pyrophosphate.

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

* * * * *

3. New Subpart D is added consisting of § 355.70 to read as follows:

Subpart D—Testing Procedures

§ 355.70 Testing procedures for fluoride dentifrice drug products.

A fluoride dentifrice drug product must meet the test requirements of any two of the following biological tests: enamel solubility reduction, fluoride uptake by enamel, and/or animal caries reduction. The testing procedures for these biological tests are on file under Docket No. 80N–0042 in the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, labeled *Bioligical Testing Procedures for Fluoride Dentifrices*, and are available or request to that office.

Alternative testing procedures may be used. Any proposed modification or alternative testing procedures shall be submitted as a petition under the rules established in § 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 subject to the disclosure rules in Part 20 of this chapter.

Dated: April 6, 1988.

Frank E. Young,

Commissioner of Food and Drugs.

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