(3) 20-minute rest period (do not towel test sites).
(4) 20 minutes moderate activity in water.
(5) Conclude water test (air dry test sites without toweling).
(6) Begin solar simulator exposure to test site areas as described in §352.73.
(b) Procedure for testing a very water resistant sunscreen product. For sunscreen products making the claim of “very water resistant,” the label SPF shall be the label SPF value determined after 80 minutes of water immersion using the following procedure for the very water resistant test:
(1) Apply sunscreen product (followed by the waiting period after application of the sunscreen product indicated on the product labeling).
(2) 20 minutes moderate activity in water.
(3) 20-minute rest period (do not towel test sites).
(4) 20 minutes moderate activity in water.
(5) 20-minute rest period (do not towel test sites).
(6) 20 minutes moderate activity in water.
(7) 20-minute rest period (do not towel test sites).
(8) 20 minutes moderate activity in water.
(9) Conclude water test (air dry test sites without toweling).
(10) Begin solar simulator exposure to test site areas as described in §352.73.

§352.77 Test modifications.
The formulation or mode of administration of certain products may require modification of the testing procedures in this subpart. In addition, alternative methods (including automated or in vitro procedures) employing the same basic procedures as those described in this subpart may be used. Any proposed modification or alternative procedure shall be submitted as a petition in accord with §10.30 of this chapter. The petition should contain data to support the modification or data demonstrating that an alternative procedure provides results of equivalent accuracy. All information submitted will be subject to the disclosure rules in part 20 of this chapter.

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

Subpart A—General Provisions

§355.1 Scope.
(a) An over-the-counter anticaries drug product in a form suitable for topical administration to the teeth is generally recognized as safe and effective and is not misbranded if it meets each condition in this part and each general condition established in §330.1 of this chapter.

§355.3 Definitions.
As used in this part:
(a) Abrasive. Solid materials that are added to dentifrices to facilitate mechanical removal of dental plaque, debris, and stain from tooth surfaces.
(b) Anhydrous glycerin. An ingredient that may be prepared by heating glycerin U.S.P. at 150 °C for 2 hours to drive off the moisture content.
(c) Anticaries drug. A drug that aids in the prevention and prophylactic
Subpart B—Active Ingredients

§ 355.10 Anticaries active ingredients.

The active ingredient of the product consists of any of the following when used in the concentration and dosage form established for each ingredient:

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

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

(3) Treatment rinses. (i) An aqueous solution of acidulated phosphate fluoride derived from sodium fluoride acidulated with a mixture of sodium phosphate, monobasic, and phosphoric acid to a level of 0.1 molar phosphate ion and a pH of 3.0 to 4.5 and which yields an effective fluoride ion concentration of 0.02 percent.

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

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

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

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

(b) Sodium monofluorophosphate—(1) Dentifrices containing 850 to 1,150 ppm theoretical total fluorine in a gel or paste dosage form. Sodium monofluorophosphate 0.654 to 0.884 percent with an available fluoride ion concentration (consisting of PO₃F²⁻ and F⁻ combined) ≥850 ppm.

(2) Dentifrices containing 1,500 ppm theoretical total fluorine in a gel or paste

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Subpart B—Active Ingredients

The active ingredient of the product consists of any of the following when used in the concentration and dosage form established for each ingredient:

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

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

(3) Treatment rinses. (i) An aqueous solution of acidulated phosphate fluoride derived from sodium fluoride acidulated with a mixture of sodium phosphate, monobasic, and phosphoric acid to a level of 0.1 molar phosphate ion and a pH of 3.0 to 4.5 and which yields an effective fluoride ion concentration of 0.02 percent.

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

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

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

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

(b) Sodium monofluorophosphate—(1) Dentifrices containing 850 to 1,150 ppm theoretical total fluorine in a gel or paste dosage form. Sodium monofluorophosphate 0.654 to 0.884 percent with an available fluoride ion concentration (consisting of PO₃F²⁻ and F⁻ combined) ≥850 ppm.

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

(3) Treatment rinses. (i) An aqueous solution of acidulated phosphate fluoride derived from sodium fluoride acidulated with a mixture of sodium phosphate, monobasic, and phosphoric acid to a level of 0.1 molar phosphate ion and a pH of 3.0 to 4.5 and which yields an effective fluoride ion concentration of 0.02 percent.

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

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

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

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

(b) Sodium monofluorophosphate—(1) Dentifrices containing 850 to 1,150 ppm theoretical total fluorine in a gel or paste dosage form. Sodium monofluorophosphate 0.654 to 0.884 percent with an available fluoride ion concentration (consisting of PO₃F²⁻ and F⁻ combined) ≥850 ppm.

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Food and Drug Administration, HHS

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Subpart B—Active Ingredients

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

(3) Treatment rinses. (i) An aqueous solution of acidulated phosphate fluoride derived from sodium fluoride acidulated with a mixture of sodium phosphate, monobasic, and phosphoric acid to a level of 0.1 molar phosphate ion and a pH of 3.0 to 4.5 and which yields an effective fluoride ion concentration of 0.02 percent.

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

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

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

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

(b) Sodium monofluorophosphate—(1) Dentifrices containing 850 to 1,150 ppm theoretical total fluorine in a gel or paste dosage form. Sodium monofluorophosphate 0.654 to 0.884 percent with an available fluoride ion concentration (consisting of PO₃F²⁻ and F⁻ combined) ≥850 ppm.

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§ 355.10

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

(3) Treatment rinses. (i) An aqueous solution of acidulated phosphate fluoride derived from sodium fluoride acidulated with a mixture of sodium phosphate, monobasic, and phosphoric acid to a level of 0.1 molar phosphate ion and a pH of 3.0 to 4.5 and which yields an effective fluoride ion concentration of 0.02 percent.

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

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

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

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

(b) Sodium monofluorophosphate—(1) Dentifrices containing 850 to 1,150 ppm theoretical total fluorine in a gel or paste dosage form. Sodium monofluorophosphate 0.654 to 0.884 percent with an available fluoride ion concentration (consisting of PO₃F²⁻ and F⁻ combined) ≥850 ppm.

(2) Dentifrices containing 1,500 ppm theoretical total fluorine in a gel or paste

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§ 355.20 Packaging conditions.

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

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

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

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

Subpart C—Labeling

§ 355.50 Labeling of anticaries drug products.

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

(b) Indication. The labeling of the product states, under the heading ‘‘Indication,’’ the following: ‘‘Aids in the prevention of dental (select one of the following: ‘‘cavities,’’ ‘‘decay,’’ ‘‘caries (decay),’’ or ‘‘caries (cavities)’’). Other truthful and nonmisleading statements, describing only the indication for use that has been established and listed in this paragraph (b), may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(i)).

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

(1) For all fluoride dentifrice (gel, paste, and powder) products. ‘‘Keep out of reach of children under 6 years of age. [highlighted in bold type] If more than used for brushing is accidentally swallowed, get medical help or contact a
Poison Control Center right away.’’ These warnings shall be used in place of the general warning statements required by §330.1(g) of this chapter.

(2) For all fluoride rinse and preventive treatment gel products. ‘‘Keep out of reach of children. [highlighted in bold type] If more than used for’’ (select appropriate word: ‘‘brushing’’ or ‘‘rinsing’’) ‘‘is accidentally swallowed, get medical help or contact a Poison Control Center right away.’’ These warnings shall be used in place of the general warning statements required by §330.1(g) of this chapter.

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

(1) For anticaries dentifrice products—

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

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

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

(2) For anticaries treatment rinse products—

(i) For acidulated phosphate fluoride solution containing 0.02 percent fluoride ion, sodium fluoride 0.05 percent, sodium fluoride concentrate, and stannous fluoride concentrate identified in §355.10(a)(3)(i), (a)(3)(iv), (a)(3)(v), and (c)(3). Adults and children 6 years of age and older: Use once a day after brushing your teeth with a toothpaste. Vigorously swish 10 milliliters of rinse between your teeth for 1 minute and then spit out. Do not swallow the rinse. Do not eat or drink for 30 minutes after rinsing. Instruct children under 12 years of age in good rinsing habits (to minimize swallowing). Supervise children as necessary until capable of using without supervision. Children under 6 years of age: Consult a dentist or doctor.

(ii) For acidulated phosphate fluoride solution containing 0.01 percent fluoride ion and sodium fluoride 0.02 percent aqueous solution identified in §355.10(a)(3)(ii) and (a)(3)(iii). Adults and children 6 years of age and older: Use twice a day after brushing your teeth with a toothpaste. Vigorously swish 10 milliliters of rinse between your teeth for 1 minute and then spit out. Do not swallow the rinse. Do not eat or drink for 30 minutes after rinsing. Instruct children under 12 years of age in good rinsing habits (to minimize swallowing). Supervise children as necessary until capable of using without supervision. Children under 6 years of age: Consult a dentist or doctor.

(3) For stannous fluoride treatment rinse products. (i) ‘‘Use immediately after preparing the rinse.’’

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

(4) For anticaries preventive treatment gel products. Adults and children 6 years of age and older: Use once a day
after brushing your teeth with a toothpaste. Apply the gel to your teeth and brush thoroughly. Allow the gel to remain on your teeth for 1 minute and then spit out. Do not swallow the gel. Do not eat or drink for 30 minutes after brushing. Instruct children under 12 years of age in the use of this product (to minimize swallowing). Supervise children as necessary until capable of using without supervision. Children under 6 years of age: consult a dentist or doctor.

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

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

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

(2) For all stannous fluoride treatment rinse, preventive treatment gel, and dentifrice products. “This product may produce surface staining of the teeth. Adequate toothbrushing may prevent these stains which are not harmful or permanent and may be removed by your dentist.”

(f) Optional additional labeling statements—(1) For fluoride treatment rinses and preventive treatment gels. The following labeling statement may appear in the required boxed area designated “APPROVED USES”: “The combined daily use of a fluoride preventive treatment” (select one of the following: “rinse” or “gel”) “and a fluoride toothpaste can help reduce the incidence of dental cavities.”

(2) For dentifrice products containing 1.500 ppm theoretical total fluorine. “Adults and children over 6 years of age may wish to use this extra-strength fluoride dentifrice if they reside in a nonfluoridated area or if they have a greater tendency to develop cavities.”

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

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

§ 355.60 Professional labeling.

(a) The labeling for anticaries fluoride treatment rinses identified in §355.10(a)(3) and (c)(3) that are specially formulated so they may be swallowed (fluoride supplements) and are provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 3 to under 14 years of age: As a supplement in areas where the water supply is nonfluoridated (less than 0.3 parts per million (ppm)), clean the teeth with a toothpaste and rinse with 5 milliliters (mL) of 0.02 percent or 10 mL of 0.01 percent fluoride ion rinse daily, then swallow. When the water supply contains 0.3 to 0.7 ppm fluoride ion, reduce the dose to 2.5 mL of 0.02 percent or 5 mL of 0.01 percent fluoride ion rinse daily.

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

Subpart D—Testing Procedures

§ 355.70 Testing procedures for fluoride dentifrice drug products.

(a) A fluoride dentifrice drug product shall meet the biological test requirements for animal caries reduction and one of the following tests: Enamel solubility reduction or fluoride enamel uptake. The testing procedures for these biological tests are labeled Biological Testing Procedures for Fluoride Dentifrices; these testing procedures are on file under Docket No. 80N-0042 in
the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and are available on request to that office.

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

(c) Alternative testing procedures may be used. Any proposed modification or alternative testing procedures shall be submitted as a petition in accord with §10.30 of this chapter. The petition should contain data to support the modification or data demonstrating that an alternative testing procedure provides results of equivalent accuracy. All information submitted will be subjected to the disclosure rules in part 20 of this chapter.

[60 FR 52507, Oct. 6, 1995, as amended at 68 FR 24879, May 9, 2003]

PART 357—MISCELLANEOUS INTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A [Reserved]

Subpart B—Anthelmintic Drug Products

Sec.
357.101 Scope.
357.103 Definition.
357.110 Anthelmintic active ingredient.
357.150 Labeling of anthelmintic drug products.
357.152 Package inserts for anthelmintic drug products.
357.180 Professional labeling.

Subpart C—Cholecystokinetic Drug Products

357.201 Scope.
357.203 Definition.
357.210 Cholecystokinetic active ingredients.
357.250 Labeling of cholecystokinetic drug products.
357.280 Professional labeling.

Subparts D–H [Reserved]